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Manganese Catalysis in Radical Coupling Reactions

Ph.D. Thesis • July 2017 • Andreas Ahlburg

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Technical University of Denmark

Manganese Catalysis in Radical Coupling Reactions

Ph.D. Thesis by Andreas Ahlburg

Preface

This thesis describes the research carried out from November 2013 to January 2017 as part of the Danish programme to obtain a Ph.D. degree. The work described herein was carried out at the Technical University of Denmark, while the work described in the appendix was carried out as part of an external stay at the company Haldor Topsøe A/S.

A list of publications resulting from the work in this thesis can be found in Appendix C.

Abstract

Transition metal catalyzed cross-couplings are an important tool in the synthetic and industrial chemist's toolbox for creating simple and complex molecules. Palladium is the most exploited metal for the catalysts but due to its price and toxicity, efforts are being directed towards finding other metals that can be used instead. Nickel is one metal that has been successful as a metal catalyst, but like another examined metal, cobalt, it is also toxic. In recent years, the focus has been on iron, a metal which is both abundant, cheap and non-toxic. The present dissertation describes the attempts to expand the conditions of the known cross-couplings to include homogeneous manganese catalysts.

In chapter 2: Manganese Catalyzed *N*-Arylation - a literature reported procedure for *N*-arylations through a non-cross-coupling mechanism was explored. The reaction proved hard to control (see graphical abstract) and gave no insights into manganese catalysis.

In chapter 3: Buchwald-Hartwig Catalyzed Cross-Couplings - a literature reported procedure was examined. It was not possible to reproduce the literature findings. Instead, the reaction was shown to be catalyzed by 10-100 ppm of a copper catalyst (see graphical abstract).

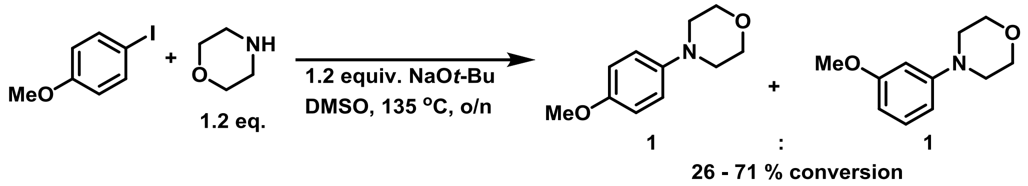
In chapter 4: Manganese Catalyzed Stille Cross-Couplings - a literature reported procedure was examined. It was not possible to reproduce the literature findings. Instead, the reaction was shown to be catalyzed by 30 ppm of a palladium catalyst (see graphical abstract).

In chapter 5: Manganese Catalyzed Kumada Cross-Couplings - a literature reported procedure was examined. The scope of this reaction was limited for the electrophile, which was attributed to an aryl radical anion intermediate that was indicated by a clock experiment (see graphical abstract).

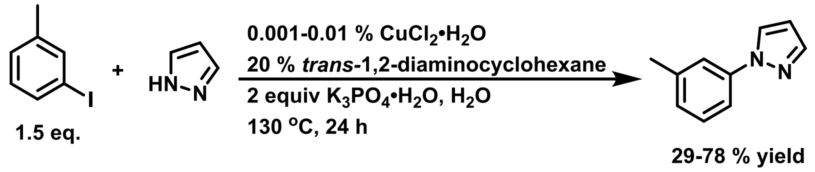
In chapter 6: Dimethyl Zinc Mediated Radical Alkylation of β-Bromostyrenes - the attempts at a manganese catalyzed Negishi cross-coupling resulted in the discovery of a radical coupling of β-bromostyrenes with ethers and tertiary amines. (see graphical abstract).

Graphical Abstract

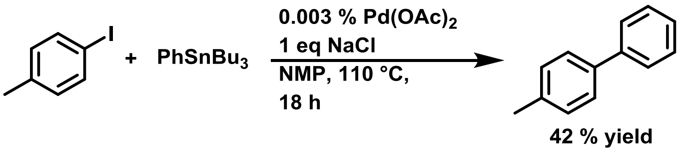
Chapter 2: Manganese Catalyzed *N*-Arylations



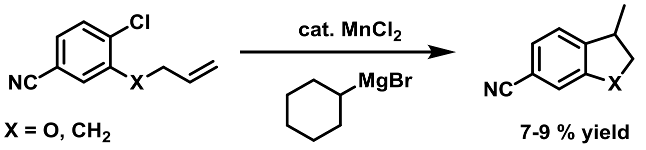
Chapter 3: Manganese Catalyzed Buchwald-Hartwig Cross-Couplings



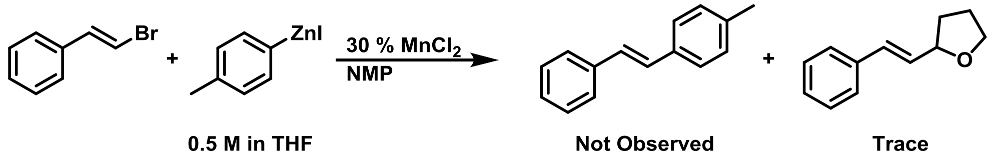
Chapter 4: Manganese Catalyzed Stille Cross-Couplings

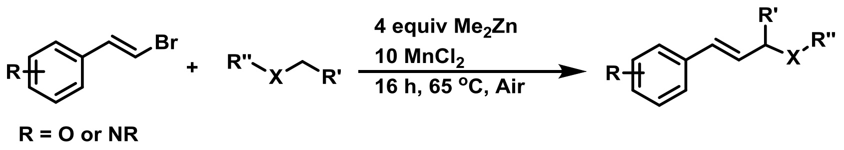


Chapter 5: Manganese Catalyzed Kumada Cross-Couplings



Chapter 6: Dimethyl Zinc Mediated Radical Alkylation of β-Bromostyrenes





Resumé

Overgangsmetal katalyserede kryds-koblinger er et vigtigt redskab for syntesekemikeren såvel som for den kemiske industri til at forme simple og komplekse molekyler. Palladium er det mest udnyttede metal i katalytiske kryds-koblinger, men på grund af metallets pris og giftighed er det blevet en udfordring at finde metaller, der kan bruges i stedet. Nikkel har haft en vis succes som katalysator, men det er også giftigt, ligesom kobolt. I senere år har fokus været på jern, et metal der findes i store mængder og er billigt og ugiftigt. Denne afhandling beskriver forsøg på at udvide betingelserne for velkendte krydskoblinger til at inkludere homogene mangan katalysatorer.

I kapitel 2: I mangan katalyserede *N*-aryleringer blev en procedure fra litteraturen undersøgt. Det er ikke muligt at kontrollere denne reaktion (se grafiske abstrakt) og de udførte eksperimenter gav ingen indsigt i mangan katalyse.

I kapitel 3: I mangan katalyserede Buchwald-Hartwig kryds-koblinger blev en procedure fra litteraturen undersøgt. Det var ikke muligt at reproducere de rapporterede resultater. I stedet blev det vist, at reaktionen finder sted med 10-100 ppm procent kobber katalysator (se grafisk abstrakt).

I kapitel 4: I mangan katalyserede Stille kryds-koblinger blev en procedure fra litteraturen undersøgt. Det var ikke muligt at reproducere disse resultater. I stedet blev det vist, at reaktionen finder sted med 30 ppm palladium katalysator (se grafisk abstrakt).

I kapitel 5: I mangan katalyserede Kumada kryds-koblinger blev en procedure fra litteraturen undersøgt. Udvalget af elektrofiler som denne reaction virkede for er begrænset. Dette blev efter mekanistiske undersøgelser, heriblandt en 'klokke'-reaktion (se grafisk abstrakt), tilskrevet et aryl anion radikal intermediat.

I kapitel 6: Forsøg på at anvende mangan i en Negishi kryds-kobling førte til en radikal kobling af β-bromostyrener med ætere og tertiære aminer (se grafisk abstrakt). Dimethylzinc medieret radikal alkylering af β-bromostyrener blev udviklet.

Acknowledgements

First, I would like to thank my supervisor Professor Robert Madsen for his help and guidance on practical and theoretical matters of organic chemistry. Thanks to Esben Taarning, Ph.D. and his colleagues for a pleasant stay at Haldor Topsøe. I would like to thank former and present members of Robert Madsen's group for the positive environment, social atmosphere, political discussions and cultural comparisons. Thanks to the Danish Council for Independent Research – Technology and Production Sciences for financial support (grant 1335-00153). Thanks to Amanda Birgitte Sølvhøj, Ph.D. and Giuseppe Antonacci, M.Sc. for collaboration. Work by my collaborators and Carola Santilli, M.Sc., are presented in this thesis as part of the larger story on 'Manganese Catalysis in Radical Coupling Reactions'. Thanks to Amanda Birgitte Sølvhøj, Ph.D. and Dominika Alina Niedbał, Ph.D., for proofreading the thesis. Finally thanks to friends and family for their patience with me during my studies.

Contents

1. Introduction

1.1. Catalysis

Jöns Jacob Berzelius[1] first came up with the name “catalysis” in 1836 when he needed a term for naming an effect that several researchers had reported earlier but had no name for. “Catalysis” was named using the same etymology scheme as “analysis” (aná, “on, up”, katá, “down”). He described catalytic power as existing in some chemicals such that their mere presence, without actual participation in the reaction, could “rouse up the play” of affinities of other compounds, otherwise inactive at that temperature, thereby caused a rearrangement of their elements. Several reinterpretations of the term were proposed over the years until the modern definition was presented by Wilhelm Ostwald at a symposium in 1901. “A catalyst is a substance that alters a chemical reaction rate without being part of the final products”.[2]

A catalyst undergoes a number of transformations during a reaction. The transformations can be chemical or conformational. To meet the prerequisite of being unaltered a regeneration of the starting material must take place. This means that a catalyst can be used in substoichiometric amounts relatively to the reagent.[3] The turnover number, TON, is an indicator of how many times a catalyst can successfully catalyze a reaction and can be calculated from equivalents of reagent divided by equivalents of catalyst assuming a full conversion of the reactant. Then multiply this number with the yield to get the actual number.

$$TON = \frac{moles\ of\ reagent}{moles\ of\ catalyst} * yield\ \%$$

Equation 1: Turnover calculation

Instead of TON, most authors often simply report the mole percentage catalyst used for a reaction.[4] In thermodynamical terms, a catalyst lowers the free energy of the highest transition state thereby increasing the reaction speed of a reaction while it does not change the energy of the reactants or the products. This means that the catalyst does not change the equilibrium of the reaction. However, enabling the reaction to be performed at the lower temperature does change the equilibrium, since the equlibrium constant is temperature dependent. A catalyst, however, does not simply lower the energy of the transition state but must coordinate to the reagent prior to the transition state and be coordinated to the product prior to the end of the reaction. For the stabilization of the intermediate to be beneficial, the effect must be larger than any stabilization of the reagent by the catalyst. If not then the activation energy becomes higher than without the would-be-catalyst. When the coordination complex of a potential catalyst and the product is lower in energy than the separated parts the reaction is mediated. Stoichiometric amounts of an additive have to be used and another reagent, or workup, is required to get the product.[3] In Figure 1 a simplified reaction coordinate of a catalyzed and an uncatalyzed reaction is depicted.

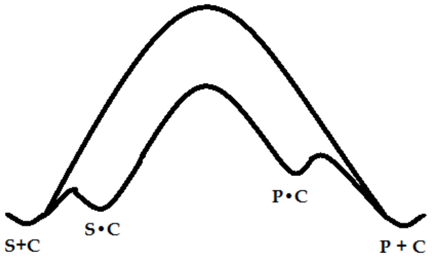


Figure 1: Simple reaction coordinate for a catalyzed and an uncatalyzed reaction.

In Figure 1 the adduct of the substrate, S, and the catalyst, C, is higher in energy than without adduct formation. The adduct of the product, P, and C is higher in energy than P and C together. With a lower transition state than the uncatalyzed reaction, C enables a catalytic reaction in the figure.

With enzymes, and sometimes transition metal catalysts, the transition state of the catalyzed reaction closely resembles the transition state of the uncatalyzed reaction. In these cases, the catalysts change the reaction mechanism, thereby facilitating the reaction. Usually organometallic catalyst change the mechanisms.[3]

1.2. Catalytic Cross-Coupling Reactions

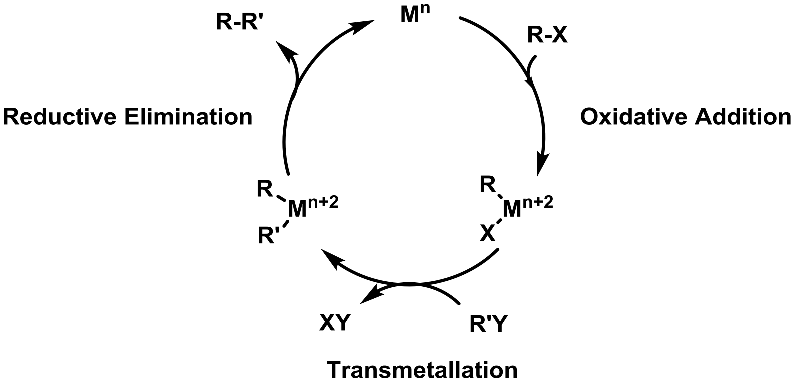
Cross-coupling reactions in general consists of a substitution of a vinylic or aromatic halide or sulfonate by a nucleophile, following the general reaction shown in Scheme 1.[3]

$$\text{R-X + M-Nu} \longrightarrow \text{R-Nu + M-X}$$

R = aryl, vinyl
X = Halide
M = Metal or Hydrogen
Nu = Carbon or Heteroatom

Scheme 1: General cross-coupling reaction.

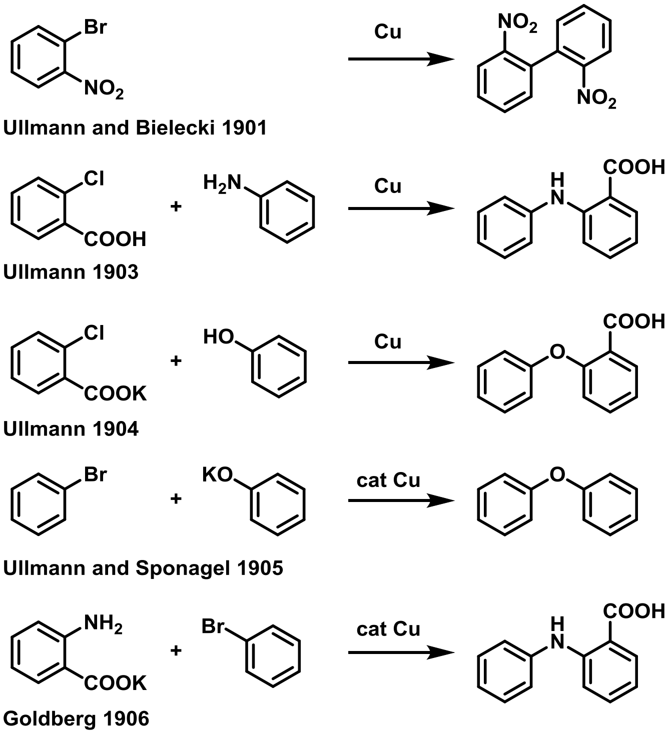
The catalytic cross-coupling involves a catalyst in the reaction mechanism leading to a repeating catalytic pathway called the catalytic cycle. For C-C bond-forming cross-couplings the nucleophile is an organometallic reagent and the simplified catalytic cycle consists of three steps, the oxidative addition, the transmetalation, and the reductive elimination.[4] The simplified catalytic cycle is show in Scheme 2.



Scheme 2: General catalytic cycle for C-C bond formations.

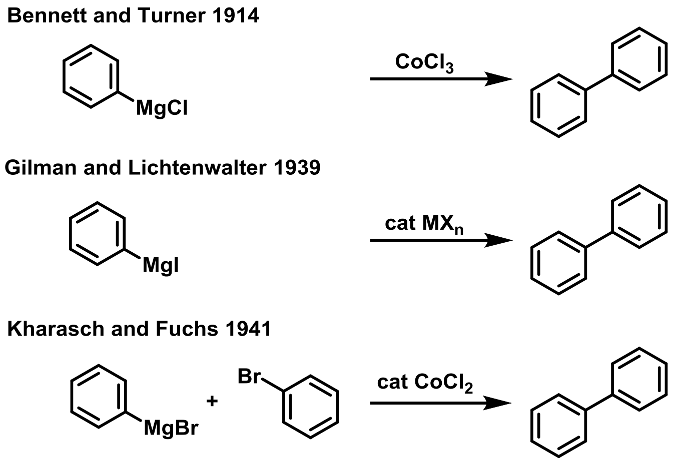
The first types of coupling reactions developed formed the homocoupling product and used stoichiometric amounts of metal, such as the bi-aryl synthesis from the coupling of various bromonitrobenzenes by Ullmann and Bielecki[5] in 1901. Two years later, Ullmann[6] used copper as a mediator for the cross-coupling of 2-bromobenzoic acid and aniline to form a C-N bond, followed by a copper mediated C-O cross-coupling of 2-chlorobenzoate and phenol in 1904[7]. These were the forerunners for the first catalytic C-O and C-N cross-couplings by Ullmann and Sponagel[8] in 1905 and Goldberg[9] in 1906, respectively. Copper catalyzed cross-couplings between an aryl halide electrophile and a phenol or aniline derived nucleophile is later referred to by variations of the name Jourdan-Ullmann-

Goldberg. The development of the copper mediated and catalyzed bond formations is illustrated in Scheme 3.



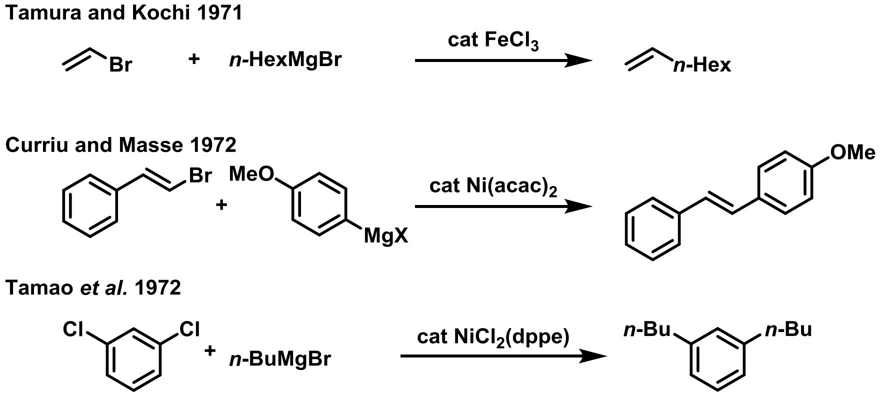
Scheme 3: Copper mediated and catalyzed bond formations.[5–9]

The next cross-coupling reaction featured magnesium halide nucleophiles, or Grignard reagents. In 1914 Bennett and Turner[10] reported a homocoupling of phenylmagnesium bromides promoted by chromium chloride including a single example of the cross-coupling product *n*-propylbenzene although only in a 3 % yield. In 1939 Gilman and Lichtenwalter[11] reported the catalytic homocoupling of phenylmagnesium iodides catalyzed by iron, cobalt, nickel, palladium and several more transition metals. The work of Kharasch and Fields[12], reported in 1941, is widely regarded as the first catalytic cross-coupling leading to a carbon-carbon bond formation. Aryl halides and aryl magnesium halides were used with cobalt(II) chloride and gave yields up to 86 %, but also manganese(II) chloride, iron(III) chloride and nickel(II) chloride gave 21 %, 47 % and 72 %, respectively. This was followed by cross-coupling products formed from phenylmagnesium bromides and alkyl[13] and vinyl[14] halides by Kharasch and coworkers in 1943. The first homo- and cross-coupling reaction with organomagnesium halides is shown in Scheme 4.



Scheme 4: First homo- and cross-couplings with organomagnesium halide species.[10–12]

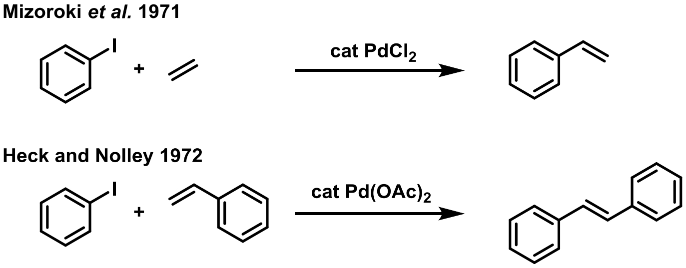
In 1971 iron was reported as a catalyst for the cross-coupling of alkylmagnesium bromides with alkyl[15] and vinyl[16] halides by Tamura and Kochi. The following year nickel catalysts were used for couplings between alkyl- and arylmagnesium bromides with alkyl-, vinyl- and arylhalides by the groups of Corriu and Masse[17] and Tamao *et al.*[18] The latter was furthermore the first to use a phosphine-based ligand in a catalytic cross-coupling reaction. The reactions are shown in Scheme 5.



Scheme 5: Iron and nickel catalyzed cross-couplings with organomagnesium nucleophiles.[16–18]

The nickel and palladium catalyzed cross-couplings between organohalides and Grignard reagents are known under variations of the name Kumada-Tamao-Corriu cross-coupling.

Meanwhile, in 1971, Mizoroki and coworkers[19] reported the first palladium catalyzed coupling of aryl iodides and ethylene. They discovered that the addition of equimolar or excessive amounts of potassium acetate would prevent polymerization of the formed styrenes. By using non-volatile vinyl compounds and tributylamine instead of potassium acetate Heck and Nolley[20] found that the reaction could be performed under milder conditions. The reactions are shown in Scheme 6.

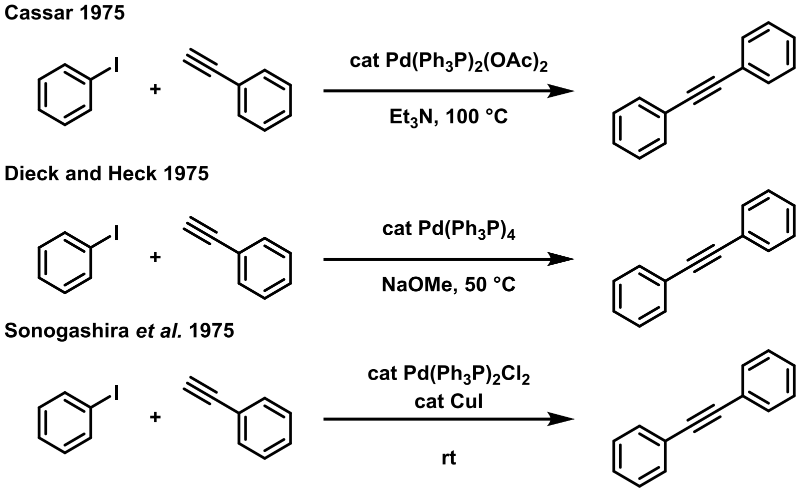


Scheme 6: Examples of the Mizoroki-Heck reaction.[19,20]

The palladium catalyzed reaction between an aryl or vinyl halide and a vinyl moiety is known as the Mizoroki-Heck reaction. While not technically a cross-coupling, since the reaction does not proceed through a transmetalation step and is terminated by a β-hydride elimination, it is often seen as such, perhaps due to its success. For example: Heck was, together with Negishi and Suzuki, awarded the 2010 Nobel prize in chemistry *"for palladium-catalyzed cross couplings in organic chemistry"*.[21]

In 1975 Yamamura and coworkers[22] used tetrakis(triphenylphosphine)palladium(0) to catalyze the cross-coupling of β-bromostyrene and vinylmagnesium bromide. With phosphine ligands to solubilize and tune the palladium catalyst, the search for the optimal catalytic metal became less pronounced and the focus shifted to find better nucleophilic coupling partners.[23]

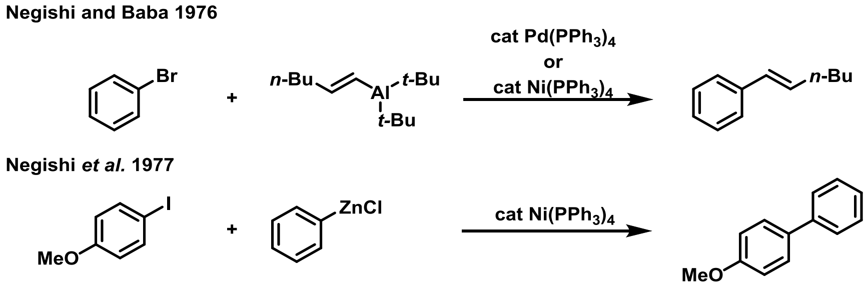
Palladium with phosphine ligands was reported three times the same year to allow for a catalytic cross-coupling with an alkyne nucleophile. Cassar[24] used sodium methoxide to activate the alkyne while Dieck and Heck[25] used tributylamine and temperatures of 100 °C. Sonogashira and coworkers[26] used a catalytic amount of copper together with diethylamine to form a copper-arylacetylene species *in-situ,* thus performing the reaction with the weaker base at room temperature. These reactions are shown in Scheme 7.



Scheme 7: Cross-couplings with alkyne nucleophiles.[24–26]

The cross-coupling using palladium and copper catalysts with an alkyne nucleophile is known as the Sonogashira-Hagihara cross-coupling.

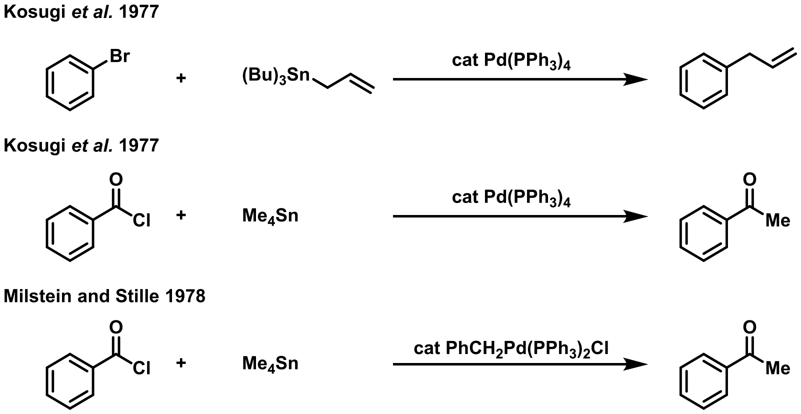
In 1976, Negishi and Baba found palladium and nickel phosphines to catalyze the coupling between aryl bromides and alkenylalanes. The following year Negishi *et al.*[27] discovered that organozinc reagents could be used as nucleophiles. The reactions are shown in Scheme 8.



Scheme 8: Organoaluminum and organozinc in cross-coupling reactions.[27,28]

Organoalanes did not become as widely known nucleophiles as the organozinc nucleophiles. The latter reaction is today known as the Negishi cross-coupling. Similarly, Negishi and van Horn[29] reported on the organozirconium nucleophiles but these did not become widespread either.

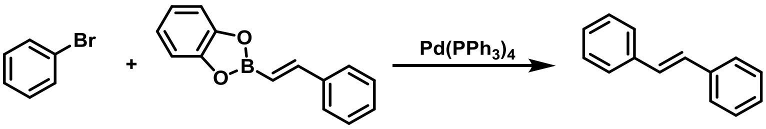
The first catalytic cross-coupling with an organostannane nucleophile was reported in 1977 by Kosugi *et al.*[30,31] using high temperatures and long reaction times. Shortly afterwards Milstein and Stille[32] improved the method and reported that trialkylstannane chloride could also be used as a nucleophile. The reactions are shown in Scheme 9.



Scheme 9: First catalytic cross-couplings with organostannane nucleophiles.[30–32]

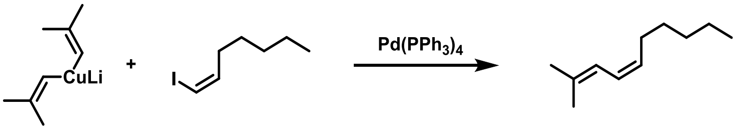
A cross-coupling reaction featuring tributylstannanyl species as the nucleophile is today often known as a Migita-Kosugi-Stille cross-coupling.

Miyaura and Suzuki[33] reported the first cross-coupling reaction with organoboron nucleophiles in 1979. This reaction, later know as the Suzuki-Miyaura cross-coupling, has been presented in more papers than any other catalytic cross-coupling reaction.[23] The reaction is shown in Scheme 10.



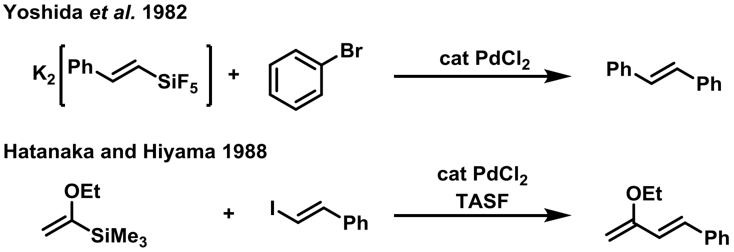
Scheme 10: Catalytic cross-coupling with organoborane nucleophile.[33]

In 1981 Jabri *et al.*[34] published the first paper where organocopper was used as a nucleophile. The reaction is shown in Scheme 11.



Scheme 11: Catalytic cross-coupling with organocuprate nucleophile.[34]

Weber *et al.*[35] reported in 1971 organosilanes as a reagent for the homocoupling using stoichiometric palladium(II) chloride. Further development by Yoshida *et al.* showed hypervalent organo(fluoro)silicates to give the cross-coupling product of allyl[36], alkenyl and aryl halides.[37] In 1988 Hatanaka and Hiyama used fluoride anions, from tris(diethylamino)sulfonium difluorotrimethylsilicate, TASF, to form the hypervalent species *in situ* thereby simplifying the procedure. The reactions are shown in Scheme 12.

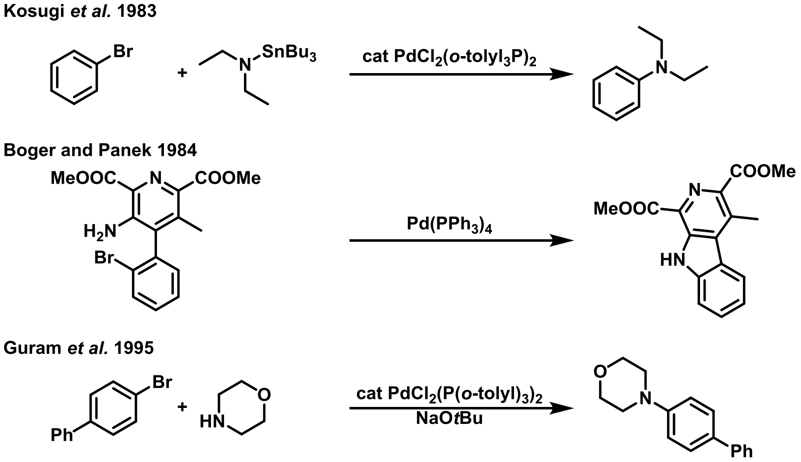


Scheme 12: Reactions with organosilicon reagents.[37,38]

Cross-couplings using organosilanes are today known as Hiyama cross-couplings.

With much of the cross-coupling chemistry developed with palladium as the catalytically active metal, attempts were made to retrace the Ullman condensation with palladium. The first palladium catalyzed C-N bond formation was reported in

1983 by Kosugi *et al.*[39] and was a variation on the Migita-Kosugi-Stille cross-coupling using an aminostannane as the nucleophile. The following year Boger and Panek formed an intramolecular C-N bond using stoichiometric amounts of tetrakis(triphenylphosphine)palladium(0). In 1995 Guram *et al.*[40] and Louie and Hartwig[41] independently reported a method for the C-N bond formation without the use of an aminostannane. Guram *et al.* used stoichiometric amounts of sodium *tert*-butoxide to promote the reaction while Louie and Hartwig used lithium bis(trimethylsilyl)amide, LiHMDS. Examples of the palladium catalyzed and promoted C-N bond formations are shown in Scheme 13.



Scheme 13: Palladium catalyzed or promoted C-N bond formations.[39,40,42]

The palladium catalyzed C-N bond formation is known as the Buchwald-Hartwig cross-coupling reaction.

When reading the literature it becomes apparent that a second definition of cross-coupling is implied. The second definition is based on the success of the reaction. According to this definition cross-coupling reactions are simply, Mizoroki-Heck, Kumada-Tamao-Corriu, Sonogashira-Hagihara, Negishi, Migita-Kosugi-Stille, Suzuki-Miyaura, Hiyama and Buchwald-Hartwig. While a literature search will reveal several articles describing modifications to 'The Mizoroki-Heck Cross-Coupling' the books on the subject are more careful in their wording. Several works of well-acknowledged scientists will not include an explanation of what a cross coupling is, but simply list these reactions.

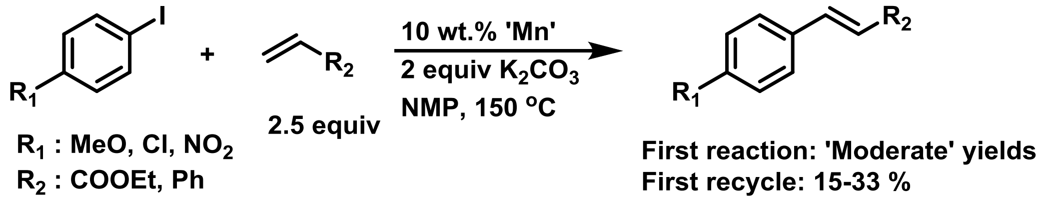
After the initial discovery of each of the famous palladium catalyzed cross-couplings the focus shifted to a continuous and ongoing fine tuning of the ligand system to accommodate more demanding electrophiles.[23] While palladium is, indisputably, superior for cross-coupling catalysis, the search for a cheaper and more benign metal substitute is the biggest challenge within the field today. However, in the search for new metals there are several pitfalls. Firstly, several metals are so finely tuned for catalysis that mere trace amounts can cause a false positive when examining the potential of another metal. Secondly, reactions with new metals might not follow a classical cross-coupling mechanism despite giving the expected products.

Two elements in the first-row transition metals are particularly interesting candidates as substitutes for palladium due to their non-toxicity and the fact that they are more environmentally benign. These metals are iron and manganese.[43] Iron has already been well established as a cross-coupling catalyst[44] while manganese has been comparatively left alone.

1.3. Manganese Catalyzed Cross-Couplings

Several manganese catalyzed cross-couplings have been reported. The Buchwald-Hartwig, Stille and Kumada cross couplings will be presented later in chapter 3, 4 and 5 respectively.

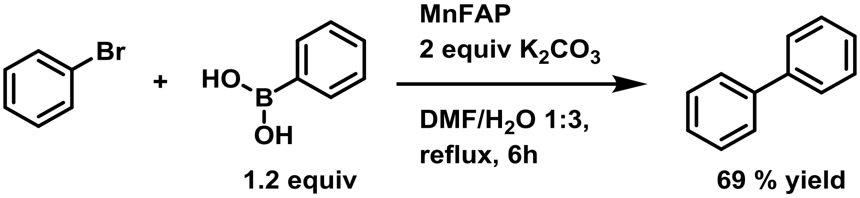
Iyer and Thakur[45] reported a manganese catalyzed Heck reaction in 2000. The preparation of the manganese catalyst follows the method for the Urushibara catalyst preparation[46] and it is reported simply as ‘Mn’. The paper reports on nickel, cobalt, copper and manganese as heterogeneous catalysts for the Heck cross-coupling, but unfortunately very little information about the manganese-catalyzed reaction is shown. X-ray photoelectron spectroscopy reports the metals to be in 0 and +1 oxidation state. The conditions are shown in Scheme 14.



Scheme 14: Heterogeneous Heck cross-coupling with manganese by Iyer and Thakur.[45]

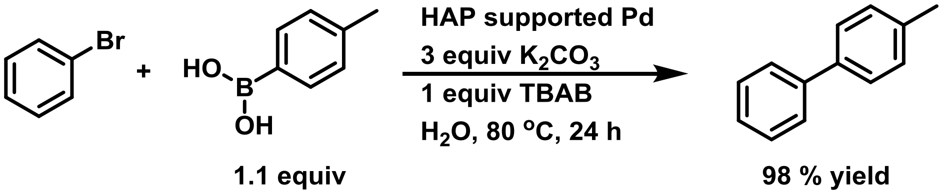
Iyer and Thakur[45] propose that the mechanism follow that of a Heck reaction. However, using methyl methacrylate, methacrolein and vinyl acetate as nucleophiles led to partial polymerization.[45] The Heck reaction usually specifically refer to a palladium catalyzed reaction with an oxidative addition, alkene coordination, insertion and β-hydride elimination. This mechanism is likewise proposed for the high temperature palladium(I)-palladium(III) ligand free heterogeneous Heck reaction.[47] The mechanism for nickel, cobalt and copper catalyzed Heck coupling was proposed to involve a reduction of the electrophile, fragmentation and addition to the alkene followed by various regenerations of the alkene.[48] What mechanism was proposed for manganese is therefore unclear as is the exact structure of the manganese catalyst. None of the articles that cite the heterogeneous manganese catalyzed Heck paper[45] exploits manganese. Instead the recent developments in this field focus on nickel, cobalt, copper, and iron.[48] Reactions where radicals add to alkenes and alkynes will be treated in later chapters.

Jiangbin *et al.*[49] reported a Suzuki cross coupling catalyzed by manganese supported on hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) in 2008. The most effective catalyst, MnFAP, was prepared from fluorideapatite and $Mn(OAc)_2$ and was heated at 60 ^{o}C in distilled water. The reaction was performed under the conditions shown in Scheme 15.



Scheme 15: Suzuki cross-coupling catalyzed by supported manganese.[49]

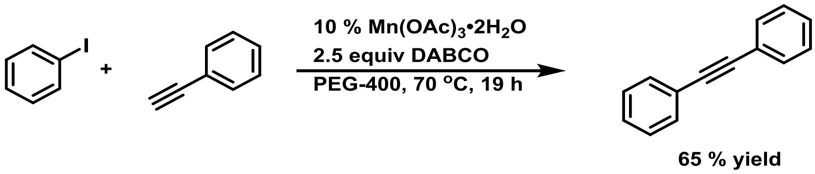
The manganese loading is around 20 %. Manganese catalyzed cross-couplings presented in this thesis will primarily be using aryl iodides as electrophiles. The aryl bromide is generally considered less reactive for cross-couplings compared to aryl iodides, so the fact that these reactions are able to handle aryl bromides emphasize their potential. When the pure hydroxyapatite was used the yield was 5 %. That the fluorideapatite and manganese(II) acetate catalyze the reaction while the metal salt and hydroapatite does not indicates that fluoride activates the manganese in the reaction. Fluoride ions in palladium catalyzed Suzuki cross couplings are well studied. Like hydroxide[50] the fluoride[51] ion activates palladium and facilitates both transmetalation and reductive elimination, while also having an antagonistic effect on the transmetalation at high concentrations. Unlike hydroxide, which shuts the reaction down at 20 or more equivalents, fluoride is still activating at 50 equivalents compared to the palladium catalyst.[50,51] For comparison, the hydroxyapatite supported palladium catalyzed Suzuki cross-couplings can be performed with 0.034 % palladium loading at 80 ^{o}C[52], shown in Scheme 16.



Scheme 16: Hydroxyapatite supported palladium catalyzed cross-coupling.[52]

Because these conditions are so similar it would have been relevant to know the purity of the manganese used. Unfortunately, the article did not mention the purity of the metal used. Again, none of the articles citing this paper are using manganese as the catalyst.

Recently, Qi *et al.*[53] reported the manganese-catalyzed Sonogashira cross-coupling. Using manganese(III) acetate dihydrate and 1,4-diazabicyclo[2,2,2]octane (DABCO) in polyethylene glycol 400 (PEG 400) at 70 ^{o}C, a number of aryl iodides were coupled with phenylacetylene. The reaction is shown in Scheme 17.



Scheme 17: Manganese catalyzed Sonogashira by Qi *et al.*[53]

Other manganese species had limited or no reactivity and similarly DABCO gave a much higher yield than other bases. This is an interesting reaction since the combination of a palladium and a copper catalyst was originally needed for the reaction to be performed below 100 °C.[26] Unfortunately, again the purity of the manganese catalyst was not included in the article. This is important since the Sonogashira cross-coupling is known to work with a number of metals and even without a catalyst. These reactions are described later.

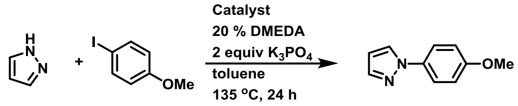
The purpose of the present thesis is to further explore the use of manganese salts as catalysts for the cross-coupling reactions and to understand the reaction mechanisms.

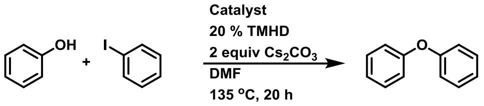
1.4. Trace Metals in Cross-Coupling Catalysis

The concept of catalysis by metal impurities is not a new phenomenon. Even before anecdotes were written about discoveries of beneficial impurities, there must have been chemists worrying about unexplained differences in their results. However, with the expanded knowledge of chemistry the issue has changed. Earlier, changes in reactivity depending on the metal batch poked the curiosity of the chemist. Since then, transition metal cross-coupling chemistry has become so well understood that when a new metal is discovered to perform such a reaction the chemist should be wary. When dealing with a new metal in these reactions another, already known to be catalytically active, metal might in fact be the active species. The change in approach have come gradually since Leadbeater and Marco[54,55] in 2003 reported the transition-metal-free Suzuki-type coupling. After they discovered that their newly reported conditions[56] for Suzuki coupling worked without any palladium they set up a 'metal free zone' in their lab to continue. New glassware and ultrapure chemicals were ordered, starting materials and products were analyzed for trace metals, specifically palladium, down to 0.5-1 ppm. After the group had moved from their laboratories, the results started to become inconsistent. This raised their suspicion that the reactivity was not fully understood.[57] Various reports of heterogeneous palladium catalyzed Heck and Suzuki couplings, where low amounts of homogeneous palladium was suspected to be the active catalyst caused the claims to be reexamined. In 2005 Arvela *et al.*[58] found that 50 ppb palladium would catalyze the reaction when using potassium carbonate as base. Similar quantities of palladium was found in the ultrapure sodium carbonate that was used for their 'palladium free' reactions. When palladium was omitted, the reaction with potassium carbonate gave less than 5 % yield. Leadbeater[57] describes one, non-scientific, school of thought of whether this actually matters, as the chemistry is still synthetically useful. However, without understanding of how the chemistry works reproducibility, optimization and error correcting are not possible. But it is not always possible to dissect these reactions. Recently Inamoto *et al.*[59] reported on a similar Suzuki-type reaction. Analysis by ICP-MS showed that the contents of palladium, nickel and copper were below 3 ppb. This reaction was not reported as 'transition metal free' but 'without adding any transition metal catalyst'.

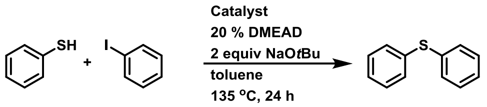
Iron catalyzed cross-couplings have been known since the early beginnings of the field. However, for many years their study have taken a backseat to other metals, specifically palladium and to some degree nickel. From the mid 90's the study of iron catalyzed cross-couplings have had a revival.[44] By 2007, the wish for finding new reactions catalyzed by iron led to the publication of several papers that were later retracted or had their claims questioned by other papers. Taillefer *et al.*[60] was the first to report on the use of iron in C-N bond formation by the Ullmann method. The reaction was an iron/copper co-catalyzed cross coupling of aryl iodides and bromides with pyrazole and other *N*-heterocycles. The coupling required both iron and copper and ran without any ligand. Correa and Bolm[61] found that copper could be omitted by using 20 % *N,N'*-dimethylethylenediamine and 10 % iron(III) chloride. This paper was followed by three more in 2008 introducing the iron catalyzed *O*-arylation[62], *S*-arylation[63], *N*-arylation of amides[64], acetanilide[65], sulfoximine[66] and *O*-arylation of amides.[67] In 2009 the groups of Buchwald and Bolm[68] independently noted that the efficiency of the iron catalyzed reaction was dependent on the purity and to an even bigger extent the commercial source of the metal. They reported various *O-, S-* and *N*-arylations with different purities and commercial sources of iron as well as reactions spiked with copper in ppm scale. The ultrapure iron(III) chloride dramatically lowered the yield and using 10-100 ppm amounts of copper(I) oxide increased the yield back to that reported previously. Around the same time Larsson *et al.*[69] examined the *N*-arylation of pyrazole and found an optimal loading of around 0.01 % copper(II) chloride. The same paper reported the *N*-arylation of sulfoximine by a 0.001 % copper loading in 51 % yield and acetanilide by a 0.1 % copper loading in 38 % yield. An overview of these reactions is shown in Table 1.

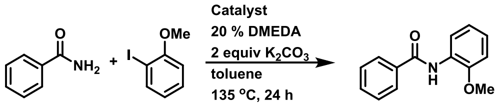
Table 1: Iron and copper catalyzed carbon-heteroatom bond formations.



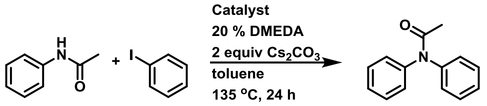


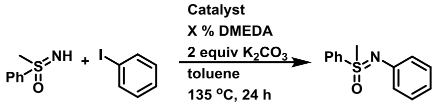
Yield	Catalyst	Reported by	Yield	Catalyst	Reported by
87 %	10 % $FeCl_3$ >98 % purity (Merck)	Correa and Bolm[61]	85 %	10 % $FeCl_3$ >98 % purity (Merck)	Bistri et al.[62]
9 %	10 % $FeCl_3$ >99.99 % purity (Aldrich)	Buchwald and Bolm[68]	32 %	10 % $FeCl_3$ >99.99 % purity (Aldrich)	Buchwald and Bolm[68]
78 %	10 % $FeCl_3$ >99.99 % purity (Aldrich) + 0.0005 % Cu_2O	Buchwald and Bolm[68]	92 %	10 % $FeCl_3$ >99.99 % purity (Aldrich) + 0.001 % Cu_2O	Buchwald and Bolm[68]
88 %	0.01 % $CuCl_2$	Larsson *et al.*[69]	87 %	0.001 % $CuCl_2$	Larsson *et al.*[69]





Yield	Catalyst	Reported by	Yield	Catalyst	Reported by
91 %	10 % $FeCl_3$ >98 % purity (Merck)	Correa *et al.*[63]	78 %	10 % $FeCl_3$ >98 % purity (Merck)	Correa *et al.*[64]
2 %	10 % $FeCl_3$ >99.99 % purity (Aldrich)	Buchwald and Bolm[68]	Trace	10 % $FeCl_3$ >99.99 % purity (Aldrich)	Buchwald and Bolm[68]
99 %	10 % $FeCl_3$ >99.99 % purity (Aldrich) + 0.01 % Cu_2O	Buchwald and Bolm[68]	97 %	10 % $FeCl_3$ >99.99 % purity (Aldrich) + 0.0005 % Cu_2O	Buchwald and Bolm[68]





Yield	Catalyst	Reported by	Yield	Catalyst	Reported by
75 %	10 % $FeCl_3$ >98 % purity (Merck)	Correa *et al.*[65]	40 %	10 % $FeCl_3$ >98 % purity (Merck), 20 % DMEDA	Correa and Bolm[66]
38 %	0.1 % CuO	Larsson *et al.*[69]	51 %	0.001 % CuO	Larsson *et al.*[69]
			45 %	20 % $FeCl_3$ >99.99 % purity (Aldrich), 40 % DMEDA	Correa and Bolm[66]

Trace metals in iron catalyzed cross-couplings were not restricted to carbon-heteroatom couplings. In 2008 the iron catalyzed Suzuki-type coupling was reported by Kylmärä *et al.*[70] using an iron-pyridine complex. Bedford *et al.*[71] attempted to reproduce the results without success. However, the reaction was shown to work with palladium(II) acetate loadings down to 1 ppm. This prompted the retraction[72] of the paper. In 2009 Bézier and Darcel[73] reported the iron(III) chloride Suzuki-type cross-coupling. After several other laboratories have had problems with reproducing their results Bézier and Darcel[74] revisited their reaction. When replacing the source of the base, potassium fluoride, the conversion disappeared leading to a retraction of their paper.

The metal catalyst in the cross-coupling of aryl halides and terminal alkynes is a more complicated story. When this coupling is co-catalyzed by a palladium and a copper catalyst it is known as the Sonogashira-Hagihara cross-coupling. Stephen and Castro[75] have reported the coupling of copper-alkynes with aryl iodides in 1963. In 1975 Sonogashira *et al*[26], Dieck and Heck[25], and Cassar[24] published on the catalytic cross-coupling. Where Dieck-Heck and Cassar used only a palladium catalyst, Sonogashira was able to lower the reaction temperature from 100 ^{0}C to room temperature by using both a palladium and a copper catalyst. In 2003 Leadbeater *et al.*[76] reported the first transition metal free Sonogashira-type coupling. The reaction was performed in a microwave oven with temperatures at 170 ^{0}C and no palladium or copper was found in the reagents or the glassware down to 1 ppm. Carril *et al.*[77] reported the iron(III) chloride catalyzed Sonogashira reaction in 2008. Gonda *et al.*[78] examined palladium impurities in the copper catalyzed Sonogashira reactions and found high conversions due to palladium contaminations in copper(I) iodide, cesium carbonate, phenylacetylene and on the stir bar. When catalyzing with copper they found down to 10 ppb palladium content to drastically increasing the reaction yield. Zuidema and Bolm[79] investigated the copper catalyzed reaction and found that there was no reactivity without copper. The reaction rate in the presence of 0.05 % copper was three times higher than at 0.5 % copper and relied on a high DMEDA loading. The effect of iron on the catalytic arylation of terminal alkynes is still being reported on, lately from 2016 by Sindhu *et al.*[80] who found no copper or palladium traces in their reagents by using ICP-MS.

With combinations of three transition metals in play and contradicting reports, it is difficult to deduce what, besides palladium and copper together, really catalyzed the reaction.

While the papers on the iron catalyzed Suzuki coupling were retracted, the papers on the carbon-heteroatom bond formation and transition metal free reactions were not. While Bolm and Leadbeater have tried to inform their peers in later papers[57,58,68,81,82] the original papers are followed by a number of papers on carbon-heteroatom couplings with iron, cobalt and manganese from other laboratories, where the authors seem to be less aware of the trace metal catalysis pitfall. Because the arylation of terminal alkynes can be performed with several different metals, combinations of the metals, and even without metals, it is difficult to separate the reasonable claims from those, which should be approached more critically. Plenio[83] sums it up: "Nonetheless, behind all of these results lingers the nagging questions as to whether the Sonogashira activity might have resulted from minute amounts of palladium impurities in certain reagents used for the cross-coupling reactions."[83]

When working with reactions where trace metal influence is suspected several actions are recommended. If a reaction is working without any added metal, the simplest approach is to purchase new chemicals. Impurities might vary from source to source but also reagents with a higher purity might have less of a metal impurity. Purifying chemicals by chromatography, recrystallization, sublimation or other techniques may be necessary, as wall as using new glassware.[57] Vollmer *et al.*[84] showed that the Teflon on the stir bar can contain metal impurities while others[69,78] report trouble of getting a blank control without new or reinforced stir bars. Hence, care should be taken with everything that is in contact with a reaction or the reagents. Having independent collaborators in other laboratories that can replicate results can also help in the way that another group will use different reagents and eliminate systematic errors in the setup. Reagents or reaction mixtures can be analyzed with inductively coupled plasma mass spectrometry (ICP-MS) which can sometimes quantify metals down to part-per-trillion level. Another useful technique is to add small quantities of the suspected metal to a reaction and see if it has any influence.[57]

When dealing with new metals where there is no or limited previous reports of a cross coupling it is tempting to turn up the temperature to observe a reaction. However, the more catalytically active metals are also more active at higher temperatures. An increase in reaction temperature should be accompanied by an increase in skepticism.

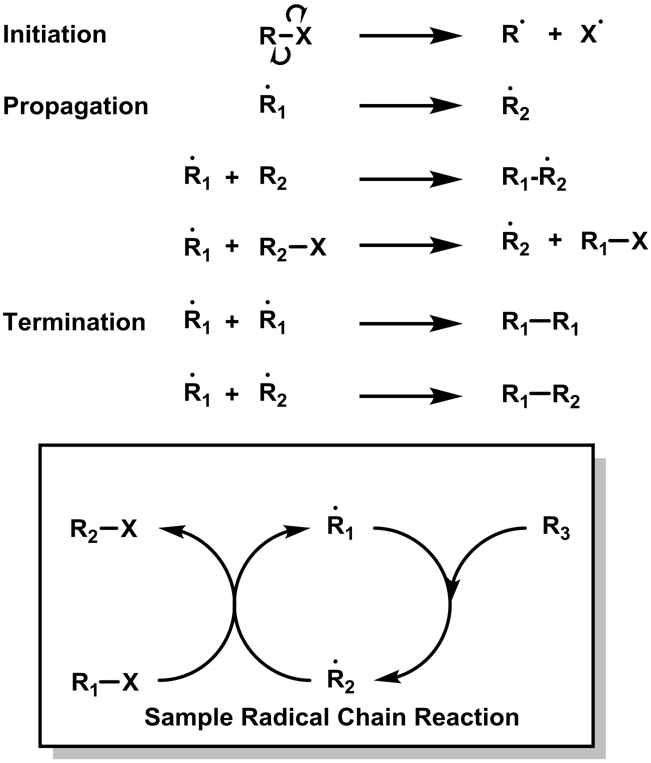
1.5. Introduction to Free Radical Chemistry

Radical reactivity can complement the traditional two-electron chemistry. While reactions with ionic intermediates often are carried out with a high or low pH environment, which can be unfeasible for acid or base sensitive molecules, radical reactions can be carried out at neutral conditions. Radicals can provide a different regioselectivity that allows functionalization at positions that would normally be inaccessible. Functional groups that normally need to be considered, such as amines, alcohols, amides and carboxylic acids are less reactive under radical conditions because of their strong N-H or O-H bonds.[85]

Free radicals exist independently of any other species and are generally very unstable. Like carbenes, carbocations and carbanions they are considered to be reactive intermediates. A radical is a molecule with an unpaired electron, usually resulting in an uneven number of electrons, with a high reactivity due to the energy that can be gained from filling the orbital by forming a new bond. There are exceptions, such as molecular oxygen, which has two radicals, an even number of electrons and is relatively stable.[85]

Radicals are involved in a number of natural processes such as autooxidation of food, ageing processes and burning, while the industrial radical processes are important in the manufacturing of polymers. Free radicals in the body can lead to arthritis and cancer, Parkinsonism and can damage arteries, leading to heart diseases or a stroke. For this reason smoking, which causes the intake of many radicals such as $NO^{\bullet}$ and $NO_2^{\bullet}$, is considered a health problem. As is exhaust fumes and ultraviolet light.[85]

Radical reactions consist of three elementary reaction steps. These steps are initiation, propagation and termination that can form either an overall chain or non-chain reaction mechanism. Both mechanisms begin with the initiation. Either the following propagation is a rearrangement of the radical compound, reacting with a non-radical to form a new radical or the radical extracts an atom from another compound creating a new radical. If there, after a number of propagation steps, is a tendency for the formation of the initiation radical, the reaction is cyclic and can be considered a radical chain reaction. When the termination, two radicals that produce a non-radical species, is the dominating reaction after propagation the radical reaction is a non-chain process.[85] The elementary as well as a sample radical chain reaction is shown in Scheme 18.



Scheme 18: Radical elementary steps.

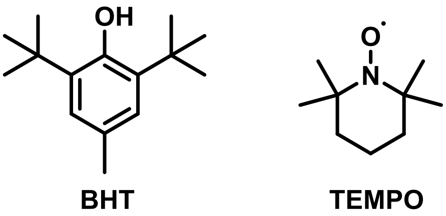
Alternatively, the radical reaction can end by redox single electron transfer forming either a cation, anion or even a neutral species if the oxidized or reduced product is sufficiently stable.[85]

With a few exceptions, radicals are very reactive intermediates that have short lifetimes. In order to cleave a bond homolytically, giving rise to two radicals, the *bond dissociation energy* (BDE) has to be determined. This energy is primarily dependent on the thermodynamic stability of the formed radicals. The homolytical cleavage of bonds to form the radicals require relatively little energy. As opposed to an ionic O-H cleavage of an acid where the solvation effect lowers the overall energy of the charged species making the deprotonation more prone to happen, radicals do not have a charge, and therefore have little interaction with solvents. Because there is no formation of a solvent shell, most radicals will form bonds with a non-radical species when they collide.[85]

Because of their short lifespan several methods for detection of radicals have been developed.[85]

Stability for alkyl radical follow the same pattern as for carbocations in the order of tertiary > secondary > primary > methyl. The order is determined by inductive, strain release and possible hyperconjugation effects. Resonance likewise contributes to the stability of a radical. Radicals centered on other atoms than carbon can be stabilized by resonance, such as a phenoxyl radical. In addition, radicals formed at the α-position of a nitrile or carbonyl are stabilized by resonance. Resonance stabilization of radicals draws parallels to carbanion resonance. However, radicals in the α-position to heteroatoms with non-bonded electrons, such as oxygen, nitrogen, sulfur, and to some extend halogens, are also stabilized through resonance. Since the resonance form is a separation of charges, the stabilization decreases as the electronegativity of the heteroatom increases. This effect is also present when the radical is centered on a heteroatom, specifically nitroxide radicals have been exploited for this effect in EPR spin trapping experiments. Generally, what stabilizes a carbanion or carbocation would also stabilize a radical, but there are exceptions. With two carbonyl groups α to a radical, one of them destabilizes the electron deficient radical more than the gained stabilization from additional resonance forms, despite mesomeric effects usually being stronger than the inductive interaction. Furthermore, combining electron withdrawing and electron donating groups enhances the stabilization of radicals contrary to what is the case with carbocations or carbanions.[85]

Because of the high reactivity of radicals, their lifetime is to a higher degree dependent on steric factors. This is exploited in additives such as butylated hydroxytoluene (BHT) which is added to stabilize foods and ether reagents, or in 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) which is used for radical inhibition.[85] These compounds are shown in Scheme 19.



Scheme 19: Butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)

When radicals are formed in the decomposing food or ether chemicals, they abstract the hydrogen of BHT, thus forming a 'persistent radical' slowing down the chain of radical reactions. TEMPO on the other hand is stored as a radical. When a reaction is retarded by the addition of TEMPO it is taken as an indication that the reaction proceeds by a radical mechanism.[85]

In radical reactions initiation is performed by heat, light or x-rays and are referred to as thermolysis, photolysis, and radiolysis, respectively. Alternatively, a redox reaction promoted by alkali metals, transition metals salts or induced by electricity can initiate these reactions. Thermolysis of alkene chains, called cracking, are done at temperatures around 600 ^{0}C, but for synthetic reactions this temperature is too high and specialized initiators are used which can reliably be homolyzed thermally at lower temperatures. Peroxides are broken at temperatures between 50 and 150 ^{0}C depending on the substituents. Initiators containing an azo group can exploit the formation of a strong N-N triple bond.[85] The most important azo initiator is azobisisobutyronitrile (AIBN), which decomposes at temperatures above 60 ^{0}C.[86] Photolysis can be done by shining visible or ultraviolet light (UV) on the molecule. A photon with the right energy can make the electrons jump from the bonding orbital to the higher energy antibonding orbital and thus breaking the bond. Photolysis has the advantage of cleaving higher energy bonds by restricting the wavelength of the light used. Peroxide and azo compounds require UV light for the bond cleavage, not because there is not enough energy present but because they are colorless and thus not able to absorb the light. Alternatives, such as molecular halogens, can be photolyzed with visible light using a non-specialized setup without a light generator and pyrex glass, that absorbs light below 320 nm. Radiolysis of organic molecules, exposing them to high-energy radiation, is relatively unselective but can be used in food processing to generate radicals that kill microorganisms. Electron transfer can also start a radical reaction. Redox reactions can be started by electricity or metals. A metal reductant or the cathode reduces the organic compound. By placing an electron in the antibonding orbital, the corresponding bond is weakened. The resulting radical is accompanied by an anion. Reversely, using a metal oxidant or anode removes an electron from the organic compound resulting in the formation of a radical and a cation.[85]

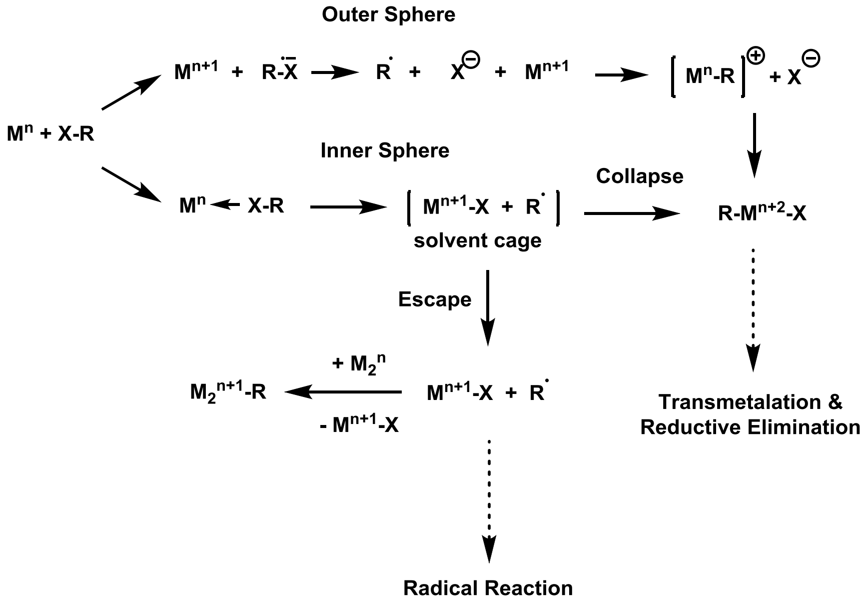
Reductions are most frequently performed by metal ions, and the most powerful among them are the alkali metals since their oxidized isoelectronic state resembles that of noble gases. Reduction of organohalides leads to the formation of an organoradical and a halide anion. Peroxides similarly lead to an alkoxy radical and an alkoxy ion. Radical generation requires that the organic species can readily decompose to form a stable radical and a cation, such as acids and alcohols. Metals that are good at oxidizing for synthetic purposes are silver(II), lead(IV), cerium(IV) and manganese(III).[85]

The reaction rates of combination reactions, where two radicals react to form a non-radical species, are diffusion controlled. The speed for reactions where radicals and non-radicals react, can vary by as much as a factor of 10^4 because entropy has a relatively greater influence. Addition and abstraction reaction rates range from 10^4 - 10^8 $dm^3\ mol^{-1}\ s^{-1}$. Generally, the less stable the radical and the more stable the product radical is the faster is the rate. For example, a phenyl radical abstracts the chloride atom from tetrachloromethane more than 100 times faster than a *tert*-butyl radical. The entropy is a positive factor for fragmentations, which is why their speed ranges from diffusion speed to around 10^5 s^{-1}. Steric effects are, when not effectively stabilizing a radical, a lesser effect. When an alkyl radical with an adjacent chiral center reacts with an alkene, a preference in reactivity for one face can occour, but such cases are exceptions. Solvent effects in radical chemistry are much less important than in reactions with ionic intermediates, but a solvent with strong bonds is preferred. This means that while water is avoided in many reactions, the strong O-H bond makes it favorable under radical conditions. Because of the high reactivity of radicals, the concentration strongly influences the reaction. When possible, neat conditions should be used, but using small amounts of solvent is otherwise recommended in order to lower the concentrations of the reagents. Slow addition of the radical precursor can likewise lower the formation of byproducts. Oxygen should be avoided when dealing with reactions that form carbon centered radicals, as it leads to hydroperoxides.[85]

1.6. Transition Metals in Radical Cross-Couplings

Radical reactions and metal catalysis potentially fit well together since the radical concentration can be kept low when it is generated by a metal catalyst. For cross-coupling reactions the effects of radicals are somewhat downplayed, because they have to follow the requirements for a cross coupling. Even when the mechanistic aspects are ignored, only few radical reactions follow the R_1-X + R_2-M → R_1-R_2 reaction scheme.[87–89] Usually, when a radical is generated, any subsequent propagation changes the structure of the R_1 or the R_2 block.[85] One exception is when a radical attacks an alkene following a propagation that reforms the alkene. However, for cross-couplings, the radical mechanism is bound to the classical cross-coupling steps. Either the steps are part radical and part two electron mechanisms or there is only the radical mechanism.

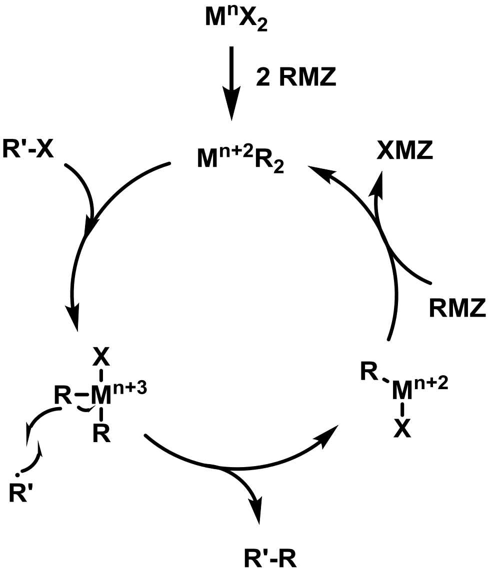
Radical oxidative additions can be done by an outer sphere or an inner sphere mechanism. The outer sphere radical oxidation starts with a SET, forming a radical anion electrophile followed by fragmentation. The organic radical might then coordinate to the oxidized metal. Coordination of the halide to the metal completes with the oxidative addition. Inner sphere radical oxidation starts with the coordination of the electrophile before the halide is extracted. Either the solvent cage containing the metal-halide and the organic radical collapses into the oxidative addition product or the radical may escape and partake in another radical pathway.[3] The radical oxidative addition is shown in Scheme 18. Oxidative additions by this mechanism lead to a racemic product mixture instead of the inversion in a S_N2 oxidative addition.



Scheme 20: Radical oxidative addition mechanisms.

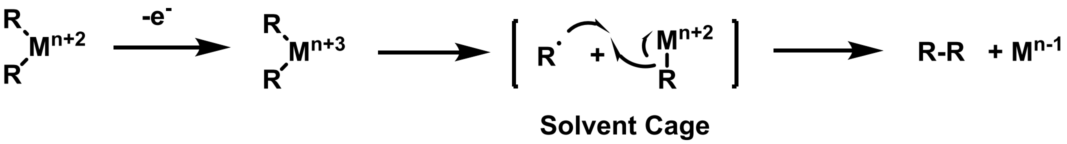
Radical oxidative addition is common among alkyl iodides and to some degree alkyl bromides. While radical oxidative additions are compatible with cross-couplings the other steps are more difficult. Transmetalations have been less well studied in general[3] and while it is possible that a radical version has been discovered, it will not be discussed in this work.

Reductive eliminations are a reverse oxidative addition. Reductive elimination to form carbon-carbon bonds occurs mostly by concerted mechanisms.[3] Some alternatives do exist. A radical species might attack another ligand leading to a ligand transfer reaction.[87] This mechanism is shown as part of a catalytic cycle in Scheme 21.



Scheme 21: Cross coupling cycle with radical ligand transfer mechanism.

Radical reductive eliminations have also been suggested to be possible when initiated by oxidation, which leads to the homolysis of a ligand bond followed by a ligand transfer.[90] The mechanism is shown in Scheme 22.

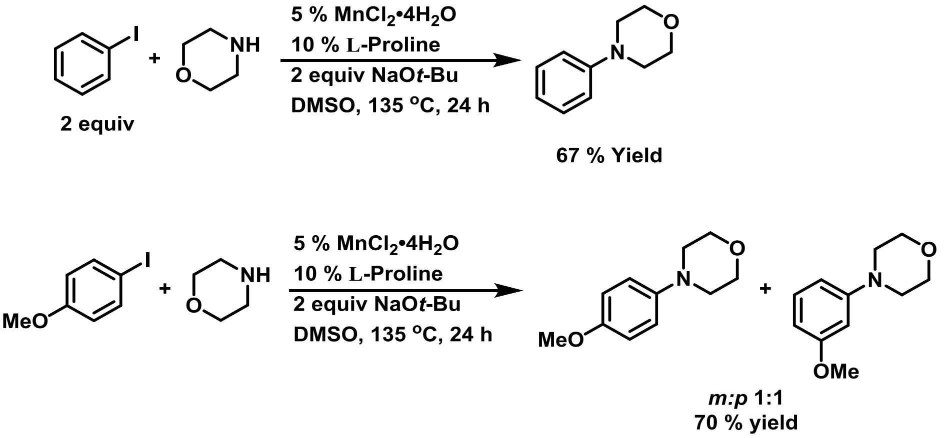


Scheme 22: Oxidation initiated radical reductive elimination.

Transition metals can have a positive interplay with radicals and while radicals can be present in oxidative additions the complete radical transition metal catalyzed cross-coupling would be hard to realize.

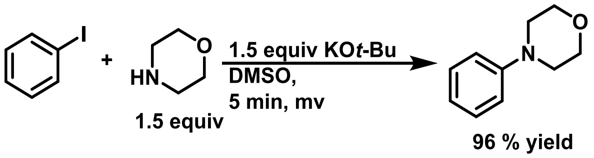
2. Manganese Catalyzed *N*-Arylations

With the view of expanding manganese-catalyzed chemistry, the C-N bond formation reaction was first considered. In 2010 Yong and Teo[91] discovered the coupling of aryl iodides with manganese(II) chloride tetrahydrate. This reaction is shown in Scheme 23.



Scheme 23: Manganese catalyzed *N*-arylation by Yong and Teo.[91]

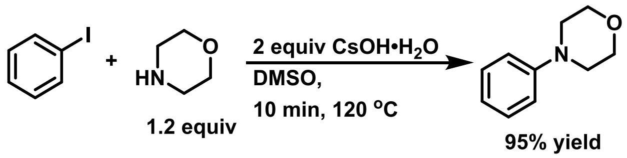
Yong and Teo stated that they used 99.99 % manganese(II) chloride tetrahydrate to exclude the participation of copper and other metal contaminations. As shown in Scheme 23, when using substituted electron rich aryl iodides the reaction products consisted of a mixture of regioisomers, indicating a possible aryne intermediate.[91] Such mixtures of products were not consistent with a catalytic cross-coupling mechanism, despite the claim in the article title. The control experiment for the reaction using no metal catalyst gave 50 % yield. Similar reactions were reported in 2003 when Shi *et al.*[92] used microwaves to promote the coupling of aryl halides with various dialkylamines using the conditions shown below in Scheme 24.



Scheme 24: Microwave assisted *N*-arylation by Shi *et al.*[92]

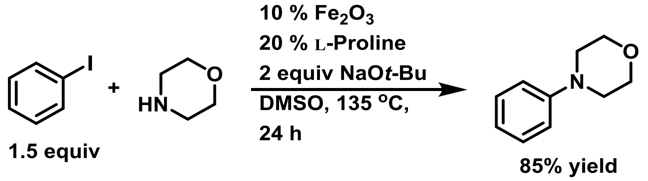
Shi *et al.*[92] noted that the reaction reached reflux temperature during the 5 minutes the microwave oven, which for DMSO would be temperatures at 188-189 °C. When using tolyl bromides the products were those expected from an aryne intermediate. The product mixtures pointed to an aryne intermediate. By adding tetrahydrofuran in the reaction the [2+4] cycloaddition product expected from an aryne was observed.[92,93]

In 2004 the reaction temperature were lowered by Varala *et al.*[94] who reported that cesium hydroxide monohydrate mediated the reaction under the conditions shown in Scheme 25.



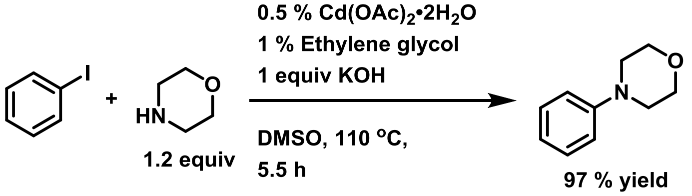
Scheme 25: Cesium hydroxide mediated *N*-arylation by Varala *et al.*[94]

Under these conditions, the reaction gave a mixture when 4-tolyl iodide was used. When cesium hydroxide was omitted no yield was observed.[94] In 2008 Guo *et al.*[95] reported the iron catalyzed *N*-arylation using the iron(III) oxide, L-proline and sodium *tert*-butoxide as shown in Scheme 26.



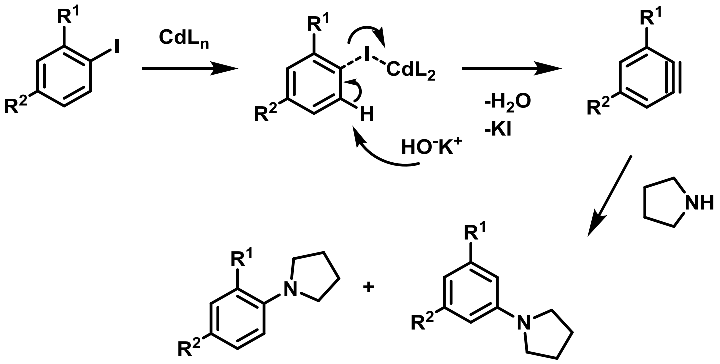
Scheme 26: Iron catalyzed *N*-arylation by Guo *et al.*[95]

Again, when the aryl halide had substituents a mixture of products was observed pointing towards an aryne intermediate mechanism. Rout *et al.*[96] reported the cross-coupling using cadmium(II) acetate dihydrate, ethylene glycol and potassium hydroxide under the conditions shown in Scheme 27.



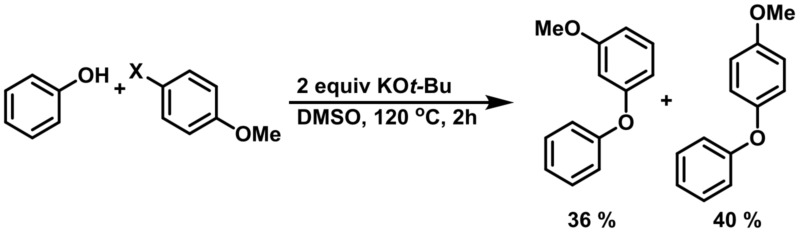
Scheme 27: *N*-Arylation with cadmium(II) acetate dihydrate by Rout *et al.*[96]

When substituted aryl iodides were used, a mixture of regioisomers was observed. The proposed mechanism for this reaction is shown in Scheme 28.



Scheme 28: Proposed mechanism for cadmium catalyzed *N*-arylation by Rout *et al.*[96]

Cadmium(II) acetate dihydrate coordinates to the halide on the electrophile and allows the base to extract a proton forming the aryne intermediate. From here addition of the amine leads to both regioisomers.[96] A similar reaction mechanism was proposed for the *O*-arylation using potassium *tert*-butoxide in DMSO at 120 °C by Yang *et al.*[97] This reaction is shown in Scheme 29.



Scheme 29: Metal and ligand free Ullmann reaction by Yang *et al.*[97]

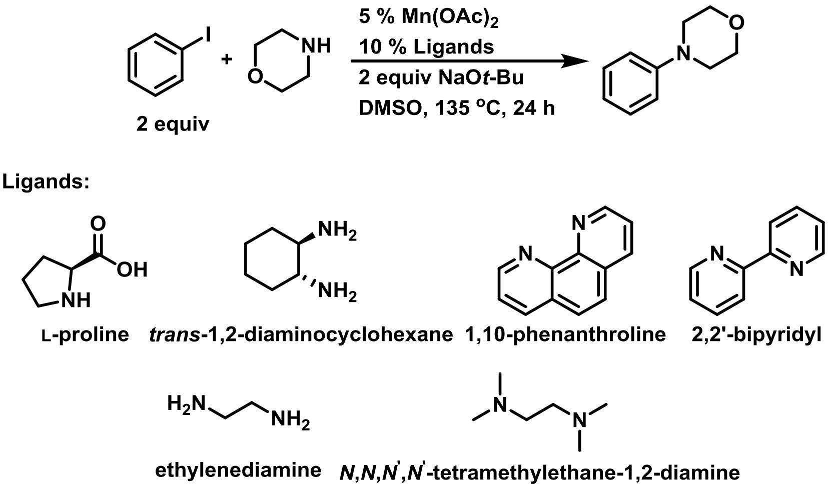
Yang *et al.*[97] included two examples of the *N*-arylation using imidazole with bromobenzene and 4-bromobenzonitrile. The reactions with these electrophiles gave a single product since they were either without a substituent or with an electron poor substituent, which likely leads to another mechanism. The authors were aware of possible interference from trace metals and had their base tested. The ICP-OES analysis showed that gold, silver, aluminum, iron, calcium, cadmium, copper, chromium, rhodium, palladium, iridium, platinum and magnesium were under the detection limit but they found a 2.5 ppm cobalt content. If an aryne intermediate can be made at 120 ^{o}C in DMSO from an electron rich aryl halide in the presence of a phenol without a metal present, it is equally feasible with morpholine as the nucleophile. The question then becomes, to what extent and how does a metal or other additives promote the reaction.

For the *N*-arylations reported by Yong and Teo[91], Shi *et al.*[92], Varala *et al.*[94], Guo *et al.*[95] and Rout *et al.*[96] the following statements are either true or not examined: A strong inorganic base or a salt of *tert*-butanol is needed. Besides DMSO the reactions can sometimes be performed in DMF with a lower yield and in one instance, with a cadmium catalyst, even toluene can be employed as the solvent.

In the present project it was decided to reinvestigate the *N*-arylations catalyzed by manganese in an attempt to expand the substrate scope and possibly to understand the mechanism.

2.1. Results

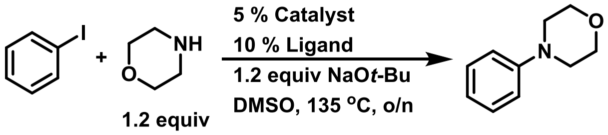
The manganese catalyzed *N*-arylation under the conditions described by Yong and Teo[91] did not meet the prerequisites of a cross-coupling reaction. Nevertheless, the reaction was selected for the initial experimental studies to get an understanding of the role of manganese in the coupling. First, the reactions were performed with manganese(II) acetate as the catalyst and a selection of diamine ligands as shown in Scheme 30.



Scheme 30: Conditions of initial testing.

This reaction has also been performed by Yong and Teo[91] with L-proline and they reported a 60 % yield. The limiting reagent for these reactions was morpholine, which did not show on the GCMS. For this reason, the conversion of the amine cannot be calculated and is not shown in any table. Instead, the reactions were evaluated by comparing the areas of the product peak with the peak of the starting material. 2,2'-Bipyridyl, a ligand not screened in the original work, performed better than L-proline. Both gave better conversions than *trans*-1,2-diaminocyclohexane, ethylenediamine, 1,10-phenanthroline and *N,N,N',N'*-tetramethylenediamine. The reaction conditions were changed such that iodobenzene was the limiting reagent for easier assessment of the conversion. Various manganese catalysts were then screened for activity. The results were evaluated on GCMS simply by comparing the percentage area of the product to that of the starting material. The screening is shown in Table 2.

Table 2: Catalyst screening in *N*-arylations.



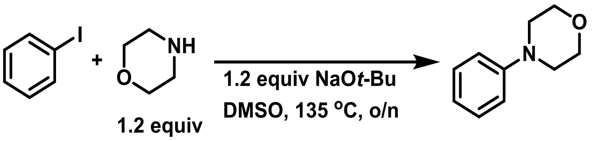
Entry	Metal	Ligand	Conversion (%)[a]
1	$Mn(OAc)_2$	L-Proline	60
2	$Mn(OAc)_2$	2,2'-bipyridyl	65
3	$MnBr_2$	2,2'-bipyridyl	65
4	$Mn(OAc)_2•2H_20$	2,2'-bipyridyl	64
5	$BrMnCO_5$	2,2'-bipyridyl	15
6	Mn_2CO_{10}	2,2'-bipyridyl	18
7	None	2,2'-bipyridyl	76
8	None	none	78

a) GCMS conversion, based on area.

The first reaction using manganese(II) acetate and L-proline gave a 60 % conversion (Entry 1) which is comparable to the 60 % yield reported by Yong and Teo[91] for the reaction with the same reagents but with morpholine as the limiting reagent. Using 2,2'-bipyridyl as the ligand gave slightly improved conversions, irrespective of the manganese(II) source, 65 %, 65 % and 64 %, respectively (entries 2-4). Using bromo pentacarbonylmanganese(I) and manganese(0) carbonyl gave low conversions of 15 % and 18 % (entries 5-6). However, the control experiments without the presence of manganese gave the highest conversions, 78 % and 76 % (entries 7-8). These results are contrary to what Yong and Teo[91] have reported and, if not merely a result of the change in the stoichiometry, suggests that the reaction might be catalyzed by impurities in DMSO at 135 ^{o}C.

To evaluate whether manganese complexes have any catalytic ability under these conditions the background reaction should be minimized. This was attempted by purifying the reagents to remove any trace metal facilitating the reaction. Iodobenzene, morpholine and DMSO were distilled into new glassware. The first experiments using such reagents and with no catalyst are shown in Table 3.

Table 3: Reaction with iodobenzene



Entry	Iodobenzene	Morpholine	NaO*t*Bu	DMSO	Conversion (%)[a]
1	Batch 1	Batch 1	Not Purified	Batch 1	54
2	Batch 1	Batch 1	Sublimated	Batch 1[b]	37
3	Batch 1	Batch 1	Sublimated	Batch 1	47
4	Batch 2	Batch 2	Sublimated	Batch 2	63

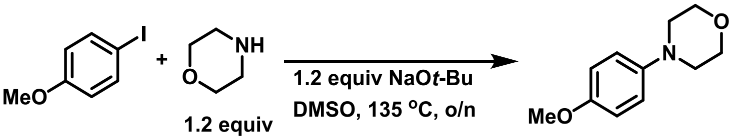
a) GCMS conversion

b) Double amounts of DMSO were used to dissolve NaO*t*Bu

The initial experiment employing distilled reagents and solvent gave 54 % conversion (Entry 1). Sodium *tert*-butoxide was sublimated onto a coldfinger that had been cleaned with hydrofluoric acid. Using the sublimated sodium *tert*-butoxide proved difficult since it could not be dissolved in the volume of DMSO used. Additional DMSO was added reducing the concentration of the reagents by half. The conversion for this reaction was 37 % (Entry 2). The sublimation of sodium *tert*-butoxide was attempted again and this time the resulting material did become a clear solution in 0.75 mL of DMSO. This reaction gave 47 % conversion (Entry 3). Sublimation of the base did lower the conversion and with this result, both iodobenzene and DMSO were distilled again in the hope that this could reduce the conversion further. Reaction with these and sublimated sodium *tert*-butoxide gave 63 % conversion (Entry 4) showing that the purification did not have the intended effect. At this point, the electrophile and the solvent batches from the first reaction had been depleted.

For ease of handling, iodobenzene was substituted with 4-iodoanisole. 4-Iodoanisole is a solid and is thus easier to weigh and transfer in accurate amounts. Also, the methoxy substituent makes it easier to evaluate the conversion by ^{1}H NMR and gives the product a higher polarity, making separation by column chromatography easier. However, because it was a solid 4-iodoanisole proved to be harder to purify. Purification was still done by distillation but cooling water could not be used because the distillate would block the condenser. It would be counterproductive to have 4-iodoanisole in contact with other chemicals, such as solvents in a recrystallization, since this would introduce other potential sources of impurities and additional parameters to control. Therefore, distillation was performed with a slightly heated condenser. Reactions with 4-iodoanisole and without catalyst are shown in Table 4.

Table 4: Reaction with 4-iodoanisole.



Entry	4-Iodoanisole	Morpholine	NaO*t*Bu	DMSO	Conversion (%)[a]
1[b]	Batch 1	Batch 1	Sublimated	Batch 2	30
2[b]	Batch 1	Batch 3	Sublimated	Batch 3	71
3[b]	Batch 2	Batch 4	Sublimated	Batch 4	47
4[b]	Batch 3	Batch 4	Sublimated	Batch 4	52
5[b]	Batch 4	Batch 4	Sublimated	Batch 4	39
6[b]	Batch 4	Batch 5	Sublimated	Batch 4	53
7[c]	Batch 5	Batch 5	Batch 1, subl.	Batch 4	27
8[c]	Batch 6	Batch 5	Batch 1, subl.	Batch 4	26
9[c]	Batch 6	Batch 5	Not Purified	Batch 4	33
10[c]	Batch 6	Batch 5	Not Purified	Batch 4	58
11[c]	Batch 6	Batch 4	Not Purified	Batch 4	59
12[c]	Batch 7	Batch 4	Not Purified	Batch 4	51
13[c]	Batch 7	Batch 4	Not Purified	Batch 4	30
14[c]	Batch 6	Batch 4	Not Purified	Batch 4	39

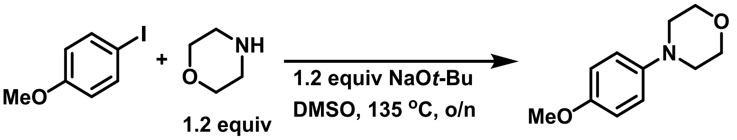
a) GCMS conversion
b) Vials rinsed with saturated potassium hydroxide in isopropanol and rinsed with deionized water.
c) Vial rinsed with saturated potassium hydroxide in isopropanol, deionized water distilled out from EDTA, *aqua regia* in 2 minutes, deionized water distilled out from EDTA, hydrofluoric acid, and finally deionized water distilled out from EDTA. A new magnet is used.

The initial reaction with 4-iodoanisole gave 30 % conversion (Entry 1). Running the reaction with new batches of morpholine and DMSO gave 71 % conversion (Entry

2). To ensure a more consistent testing of the starting materials a larger batch of both morpholine and DMSO was prepared. The reactions with these and various batches of 4-iodoanisole gave from 39-52 % conversion (Entry 3-5). Changing the batch of morpholine gave 53 % conversion. The purification of the vials was changed to a more thorough procedure and a new batch of 4-iodoanisole was distilled from a mixture containing EDTA and potassium hydroxide. The reaction with this new cleaning procedure gave 27 % conversion (Entry 7). This conversion was lower than in any of the previous reactions. This reaction protocol was repeated with a new batch of 4-iodoanisole distilled from EDTA and potassium hydroxide, giving 26 % conversion (Entry 8). Since sodium *tert*-butoxide have to be sublimated for each reaction and the batches were not entirely consistent, the reaction was tested with a base that has not been sublimated. This reaction gave 33% conversion (Entry 9). Since this was only a slightly higher conversion, non-sublimated sodium *tert*-butoxide have been used for further reactions until other parameters were controlled. Different cleaning methods and different methods for purification of the reagents were tested and during these tests, the conversion slowly increased without any apparent explanation. These experiments are not shown in the table. Entry 10, 58% conversion, is an attempt to reproduce the exact condition of Entry 9, 33 % conversion. That these experiments have a difference of 25 % could indicate that perhaps there is a factor not accounted for. The reactions were repeated as shown in Entry 11, resulting in 59 % conversion. Again, several experiments were performed where the reagents were systematically exchanged to try to find an impurity by virtue of elimination. These experiments were not successful and therefore left out of the table. The experiments in Entry 12 and 13 show the same reaction using the same batches of reagents but with conversions of 51 % and 30 %, respectively. Between these reactions, the saturated potassium hydroxide in isopropanol and the water used for rinsing the vials during cleaning have been changed. From retrospect, it was suspected that the rise in conversion between Entry 9 and 10 has perhaps been caused by a change in the water used for cleaning. The reaction was repeated using 4-iodoanisole and the conditions from Entry 9. This reaction gave 39 % conversion (Entry 14). These reactions are included to give an impression of how difficult the reaction is to control.

With this inconsistency in results, the method for cleaning the glassware was evaluated. The reagents and cleaning batches were the same as in Table 4, Entry 13. The procedure for cleaning the glassware was altered to observe if one of the methods were superior. In addition, the glassware used was numbered to observe how each vial performed over multiple reactions. The results for this are shown in Table 5.

Table 5: Screening of the glassware cleaning method.



Entry[a]	Cleaning method	Glass Nr.	Conversion (%)[b]
1	*Aqua Regia*, HF, KOH and isopropanol	1	55
2	HF, *Aqua Regia*, KOH and isopropanol	2	44
3	*Aqua Regia*, KOH and isopropanol, HF	3	26
4	KOH and isopropanol, HF, *Aqua Regia*	4	32
5	*Aqua Regia*, KOH and isopropanol, HF	1	49
6	*Aqua Regia*, KOH and isopropanol, HF	2	46
7	*Aqua Regia*, KOH and isopropanol, HF	3	48
8	*Aqua Regia*, KOH and isopropanol, HF	4	35

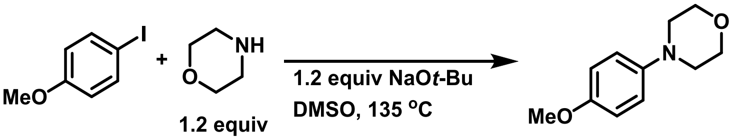
a) 4-iodoanisole batch 7, morpholine batch 4, DMSO batch 4

b) GCMS conversion

The results indicated that the cleaning method in Entry 3 was superior. However, when the cleaning method was applied to all vials the reactions showed higher conversions (entries 5-8). The reaction with the largest change in conversion was vial no. 3 that has already been used with this cleaning method. From these results, it was not possible to give any correlation between the cleaning method and the glassware. However, the experiments showed again the great variation of the performance under strict control of the parameters.

Since it proved impossible to establish a baseline for the reaction another strategy was attempted. If the reaction time was lowered, the background reaction would decrease, which would perhaps make it easier to observe catalysis from metals that would be added to the reaction. The reaction glassware was changed to single use microwave vials thus eliminating the purification steps, and furthermore the magnets where left out. The quantification of the conversion was performed by ^{1}H NMR from this point on. The correlation between the reaction time and the conversion is shown in Table 6.

Table 6: *N*-arylation in new glassware.



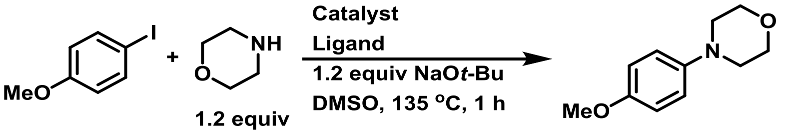
Entry	4-Iodoanisole	Morpholine	DMSO	Reaction Time	Conversion (%)[a]
1	Batch 7	Batch 4	Batch 4	Over night	57
2	Batch 7	Batch 5	Batch 4	Over night	57
3	Batch 7	Batch 5	Batch 3	30 min	19
4	Batch 7	Batch 5	Batch 3	60 min	28
5	Batch 7	Batch 5	Batch 3	120 min	44
6	Batch 7	Batch 5	Batch 5	30 min	12
7	Batch 7	Batch 5	Batch 5	60 min	19
8	Batch 7	Batch 6	Batch 5	30 min	9
9	Batch 7	Batch 6	Batch 5	60 min	22

a) ^{1}H NMR conversion

The experiment where the reaction was run overnight gave 57 % conversion (Entry 1). This experiment had similar reagent batches to those shown in Table 4, Entry 12 and 13. Despite the different ways of quantifying the conversion, these experiments gave comparable results. The reaction was repeated with a new batch of morpholine, resulting again in 57 % conversion (Entry 2). The comparable conversion of these reactions despite changing morpholine indicated that new glassware for each reaction could stabilize the conversion. After subsequently running many reactions with identical conditions but obtaining different results, one must conclude that this correlation might have been coincidental. Using the same reagents as in Entry 2, the reaction was repeated with 30, 60 and 120 min reaction time giving 19 %, 28 % and 44 % conversion, respectively (Entries 3-5). The DMSO batch was replaced and the reactions were repeated for 30 and 60 minutes giving 12 % and 19 % conversion, respectively (Entry 6 and 7). Similarly, morpholine had been prepared in an insufficient quantity and a larger batch was prepared. The reactions were repeated using reaction times of 30 and 60 minutes giving 9 % and 22 % conversion, respectively (Entry 8 and 9). With the lower reaction times, conversions and discrepancies in conversions became much smaller as expected.

With a low and relatively consistent conversion of the reaction, attempts were made to spike the reaction with copper impurities and diamine ligands to observe how this would affect the reaction. These reactions are shown in Table 7.

Table 7: Screening of catalyst and ligands in *N*-arylations.



Entry[a]	Metal and Ligand	Conversion (%)[b]
1	0.002 % CuI	19
2	0.2 % CuI	19
3	1.7 % CuI	19
4	1.6 % CuO	19
5	1.2 % $CuCl_2 \bullet 2H_2O$	12
6	4 % CuI + 10 % *trans*-1,2-diaminocyclohexane	13
7	4 % CuI + 9 % *N,N'*-Dimethylethylenediamine	17
8	0.002 % CuI + 7 % Tetramethylethylenediamine	16
9	1 % Tetramethylethylenediamine	15
10	1 % NiO	24
11	1 % $NiCl_2$	20
12	1.4 % $FeCl_2 \bullet 4H_2O$	7
13	1.5 % $FeCl_3 \bullet 6H_2O$	17
14	1.4 % Fe_2O_3	18
15	2.4 % MnO_2	19
16	8 % $MnCl_2$	16
17	7 % $MnCl_2$ + 10 % *trans*-1,2-diaminocyclohexane	11

a) 4-iodoanisole batch 6, morpholine batch 6, DMSO batch 5

b) ^1H NMR conversion

Using different amounts of copper(I) iodide from 0.002 % to 1.7 % gave a consistent conversion of 19 % (entries 1-3). Using 1.6 % copper(II) oxide similarly gave 19 % conversion (Entry 4). When copper(II) chloride dihydrate was used, only 12 % conversion was obtained (Entry 5). Using 4 % copper(I) iodide with 10 % *trans*-1,2-diaminocyclohexane and 9 % *N,N'*-dimethylethylenediamine gave 13 % and 17 % conversion, respectively (entries 6 and 7). Using a low copper(I) iodide loading of 0.002 % copper(I) iodide and 7 % tetramethylethylenediamine gave 16 % conversion (Entry 8), while leaving the copper metal out and adding 1 % of tetramethylethylenediamine (Entry 9) gave 15 % conversion. The reactions with 1 % nickel(II) oxide and nickel(II) chloride gave 24 % and 20 % conversion, respectively (entries 10 and 11). 1.4 % Iron(II) chloride tetrahydrate gave 7 % conversion (Entry 12), while 1.5 % iron(III) chloride hexahydrate and 1.4 % iron(III) oxide gave 17 % and 18 % conversion, respectively (entries 13 and 14). Finally, the reactions with 2.4 % manganese(IV) oxide gave 19 % conversion (Entry 15), while the reaction with 8 % manganese(II) chloride and 7 % manganese(II) chloride with 10 % tretramethylethylenediamine gave 16 % and 11 % conversion, respectively (entries 16 and 17). The results in Table 7 show that the reactions with 1 hour reaction time with copper, nickel, iron and manganese catalysts had comparable yields to the reaction without metal.

2.2. Discussion

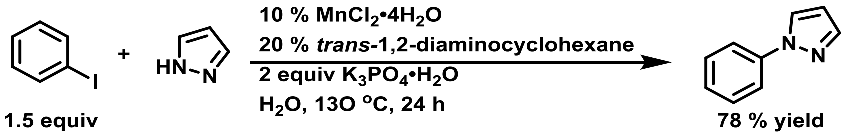
Samples of reagents and solvent were sent to ICP-MS metal analysis at ALS Global. The metals examined for were nickel, iron, manganese, cobalt, palladium, platinum, and copper. 4-Iodoanisole batch 6 contained traces of palladium (2.31 mg/kg), iron (1.06 mg/kg), and manganese (4.2 mg/kg). Sodium *tert*-butoxide batch 4 contained iron (0.561 mg/kg). DMSO batch 4 contained nickel (0.0182 mg/kg). Morpholine batch 4 did not contain any of the metals. These reagents were used in the reaction in Table 4 Entry 14 (39 % conversion). The palladium content can be calculated to be around 0.00005 % for this reaction. Reactions with added copper, nickel, iron and manganese (Table 7, entries 1-8 and 10-17) indicated that the impurities did not affect the conversion. The reaction reported by Yong and Teo[91] is difficult to suppress even when using no catalyst or ligand.

2.3. Conclusion

Probing for the catalytic ability of manganese metal in the *N*-arylation in DMSO at 135 ^{0}C was not successful. It was not possible to hinder the background reaction or even get stable conversions. When the reaction time was lowered to establish a baseline for the reaction, neither copper, nickel, iron nor manganese gave any noticeable additional conversion. Consequently, the reaction reported by Yong and Teo[91] is clearly not catalyzed by manganese.

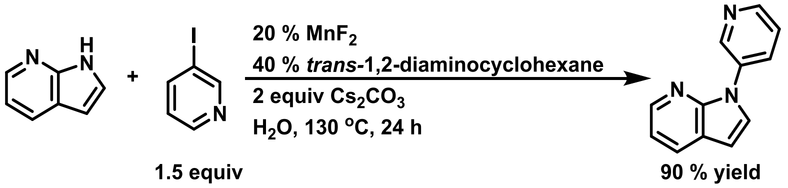
3. Manganese Catalyzed Buchwald-Hartwig Cross-Coupling

Despite the initial experiments of the manganese-catalyzed C-N bond formation were not successful there was still a number of reactions that could be examined to improve the understanding of this coupling. A manganese catalyzed C-N bond formation that closer resembles what would be expected from a classic metal catalyzed cross-coupling was reported in 2009 by Teo *et al.*[98] The cross-coupling of iodobenzene and pyrazole in water is shown in Scheme 31.



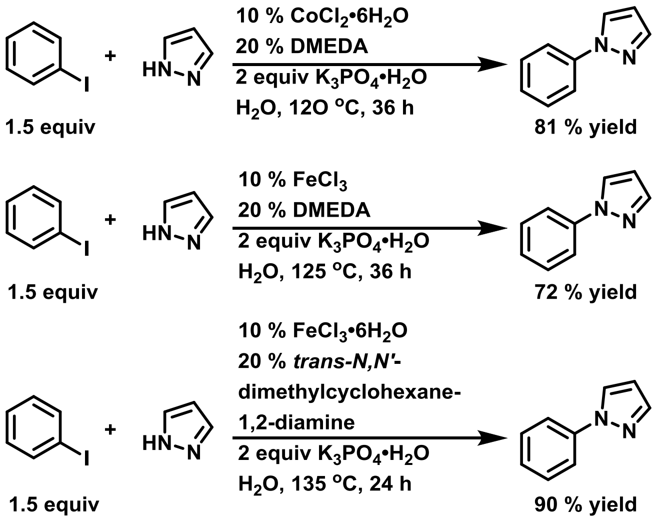
Scheme 31: Manganese catalyzed *N*-arylation in water by Teo *et al.*[98]

Control experiments without catalyst or amine ligand gave no product and the manganese source was reported to be of 99 % purity from Sigma Aldrich.[98] Unfortunately, the control experiment was performed with dipivaloylmethane, instead of *trans*-1,2-diaminocyclohexane, a ligand that did not give any product when used with manganese(II) chloride tetrahydrate. Another control was performed by using their optimized reaction conditions with a 99.99 % pure manganese(II) chloride tetrahydrate from Sigma Aldrich giving an isolated yield of 64 %.[98] The scope of this reaction was expanded in 2012 when Yong and Teo[99] coupled indole derivatives with activated aryl iodides under similar conditions as shown in Scheme 32.



Scheme 32: Manganese catalyzed *N*-arylation in water by Yong and Teo.[99]

This reaction was also performed with manganese(II) chloride tetrahydrate giving comparable yields. Control experiments using no metal gave only a 6 % yield and the reaction with potassium phosphate as a base gave 26 % yield. The source of manganese(II) fluoride was reported to be of 98 % purity. In addition to the reported manganese catalyst, cobalt was similarly reported to be a catalyst for the reaction by Teo and Chua.[100] Iron was reported by both Teo[101] and Lee *et al.*[102] Cobalt and iron as catalysts were reported in 2009 and the conditions are shown in Scheme 33.

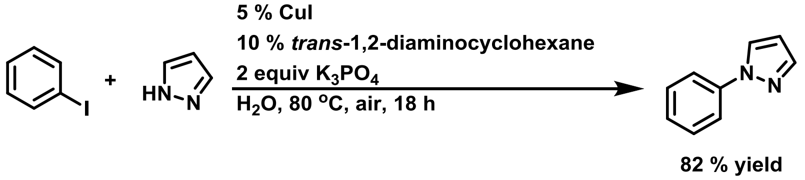


Scheme 33: Cobalt and iron catalyzed C-N cross-coupling by Teo and Chua[100], Teo[101] and Lee *et al.*[102]

The four reactions had ligands that gave good yields with some of the metals and no reactivity with others. However, *trans*-1,2-diaminocyclohexane was used as the ligand in all the papers shown in Scheme 33 and gave between 58 % and 78 % yield.

The fact that the reaction can be catalyzed by three different metals under the same conditions could be an indicator that a trace metal could be responsible. The control experiments for the above reactions whether with or without a metal, ligand or both gave no product. It was noted that the cobalt and iron reactions reported by Teo and Chua[100] and Teo[101] were catalyzed with 98 % pure metal catalyst.

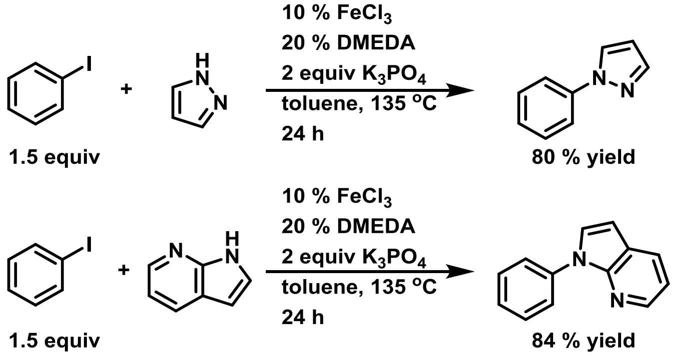
The copper catalyzed *N*-arylation of aryl iodides was reported in 2010 by Swapna *et al.*[103] using the conditions shown in Scheme 34. The reaction under these conditions required only 80 °C, 40-55 °C less than the reactions catalyzed by manganese, cobalt or iron.[98,100–102]



Scheme 34: Copper catalyzed *N*-arylation by Swapna *et al.*[103]

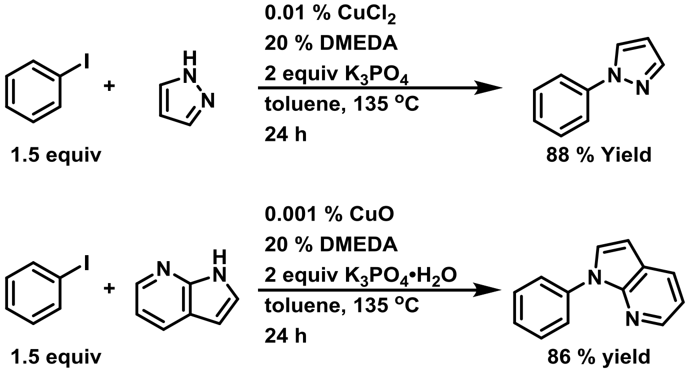
The efficient copper catalyzed cross coupling of aryl iodides and pyrazole in water raised the question of how miniscule amounts of copper are necessary to catalyze the reaction at 120-135 °C. It is possible that a 98 % pure catalyst of another metal might contain sufficient impurities of copper to catalyze the reaction.

Trace copper catalysis is exemplified by the similar reaction in toluene. In 2007 Correa and Bolm[61] reported the iron(III) chloride catalyzed reaction using toluene as the solvent. The conditions are shown in Scheme 35.



Scheme 35: Iron catalyzed *N*-arylation by Correa and Bolm[61]

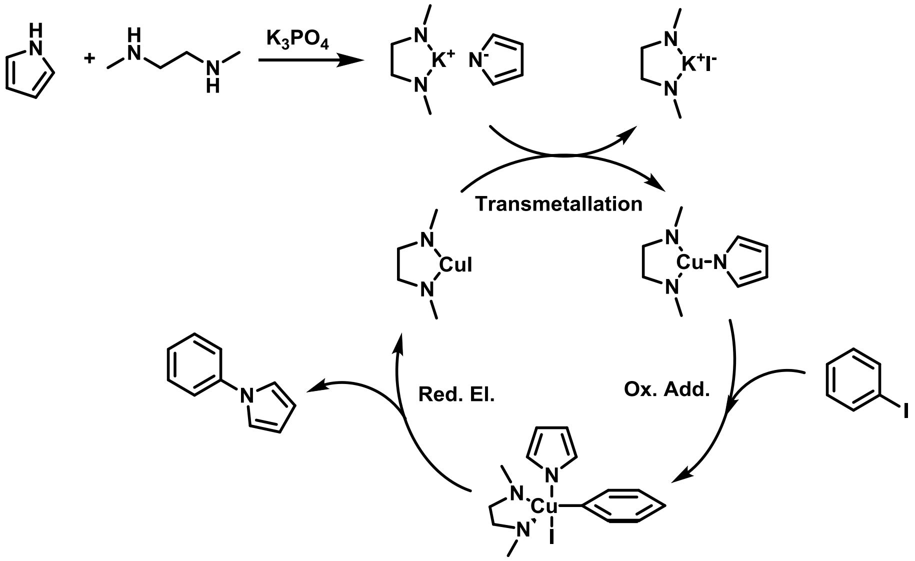
The control reactions without either ligand or metal gave no yield and the metal purity was 98 %. In 2009 Larsson *et al.*[104] investigated this reaction with a low catalyst loading and examples of these reactions are shown in Scheme 36.



Scheme 36: Copper catalyzed *N*-arylation by Larsson *et al.*[104]

Another approach to these reactions was reported by Buchwald and Bolm.[68] They reported that the conversion relied on the purity of the iron(III) chloride, i.e. that 98 % purity resulted in 87 % conversion while 99.99 % iron(III) chloride gave 9 % conversion. Atom absorption spectroscopy indicated that the 98 % pure iron contained 0.034 % copper. In addition, it was noted that the major contaminant was manganese (0.17 %) and control experiments with manganese showed that this was not catalytically active. Similarly, Buchwald and Bolm[68] observed that spiking the reactions of 99.99 % pure iron(III) chloride with 5 or 10 ppm copper(I) oxide gave the same results as the reaction with only the low copper loadings.

The reaction catalyzed by copper in toluene with DMEDA was studied by Larsson *et al.*[69] using pyrrole as the nucleophile, and the catalytic cycle is shown in Scheme 37.

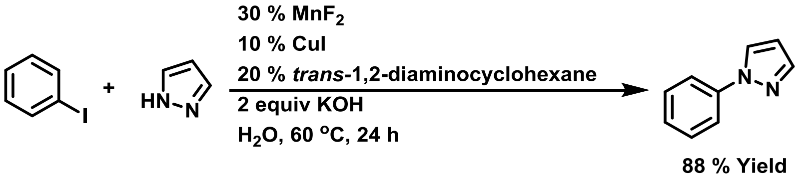


Scheme 37: Catalytic cycle of a submol % copper catalyzed reaction by Larsson *et al.*[69]

They proposed a mechanism where DMEDA solubilized the deprotonated nucleophile before the transmetalation. The formation of the transmetalated complex is in an unfavorable equilibrium that leads to the high reaction temperatures and reaction time. Oxidative addition, which is often the rate determining step in the cross-coupling reaction, of aryl iodide to DMEDA-Cu-Nu was calculated to proceed even below room temperature.[69] Such low temperatures have not been reported, but a reaction with pyrazole in neat DMEDA at 65 ^{0}C gave 88 % yield after 16 hours, using 0.01 % copper(II) chloride.[82] Higher loadings of copper bind more of the ligand, meaning that less nucleophile is available in the reaction due to it being solvated. Furthermore, when the ratio of diamine to copper gets low enough, an equilibrium between copper and an inactive copper species coordinated with two nucleophiles becomes a limiting factor.[69,105]

Reactions with low copper loadings in water were not discovered in a literature search. As previously stated, the manganese, cobalt and iron catalyzed reactions in water had control experiments which gave no product except in one case where the control experiment gave 6 %.[98–102] However, the original report on the iron catalyzed reaction in toluene had two control experiments giving no product.[61] Because copper traces in iron were sufficient to catalyze the reaction run in toluene, the same could be the case for the manganese-catalyzed reactions. The fact that the control experiments gave no product in such sensitive reactions is worrying in the first place when considering that 0 % yield control experiments were difficult to get due to something a trivial as magnetic stir bars with a too thin Teflon coating.[69] To understand the catalytic potential of manganese, the sensitivity of the reaction with regard to copper impurities must be better understood.

Teo and coworkers[106] improved the manganese catalyzed reaction, by combining manganese and copper as a bicatalytic system, where the temperature could be lowered to 60 °C. The conditions are shown are Scheme 38.



Scheme 38: Bimetallic catalyzed *N*-arylation by Teo and coworkers.[106]

The scope of these reactions was expanded by Teo and other coworkers[107] by using amides and sulfonamides as nucleophiles. The control experiments for these reactions showed that leaving copper out gave no product and leaving manganese out resulted in 24 % yield.[106]

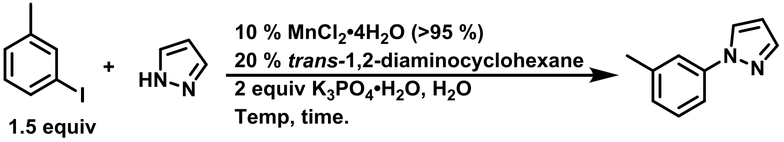
3.1. Results

Experiments with the manganese catalyzed reaction in water had to clarify several points. Because 10 ppm copper catalyst have been used to catalyze the reaction in toluene, it was necessary to validate that the reaction was indeed catalyzed by manganese. As part of this, it would be necessary to know how little copper could catalyze the reaction.

Initially the reaction reported by Teo *et al.*[98] with manganese(II) chloride tetrahydrate was examined, using the reported optimized conditions. 3-Iodotoluene was selected as the electrophile for several reasons. Firstly, the product mixture of regioisomers was not reported for neither the manganese, cobalt or iron catalyzed reactions.[98–102] Nevertheless, an electrophile with a substituent would ensure that benzyne intermediates were not formed during the reaction. Secondly, the electrophile should allow for easy purification, and therefore 4-iodoanisole was replaced since the vacuum distillation of this compound needed careful handling. Finally, the starting material and potential products should be easily observed and quantified using NMR spectroscopy. Reactions with this substrate gave 75 % yield with both manganese[98] and cobalt[100] catalysts in the respective papers and 74 % with iron.[101]

New microwave glass vials and stir bars were used for each reaction. The chemicals were used without further purification except for the solvent, which was deionized water distilled once. The reactions are shown in Table 8.

Table 8: Reproduction of manganese catalyzed arylation.



Entry	Temp. (°C)	Time (h)	H_2O[a]	Stir bar	Yield (%)[b]
1	135	21	DI	Yes	16[c]
2	135	21	DI	No	22
3	130	24	DI	Yes	11[d]
4	130	24	DI	No	12
5	130	24	Tap	Yes	45

a) DI: Deionized water, distilled once. Tap: Water from the tap

b) Isolated yield.

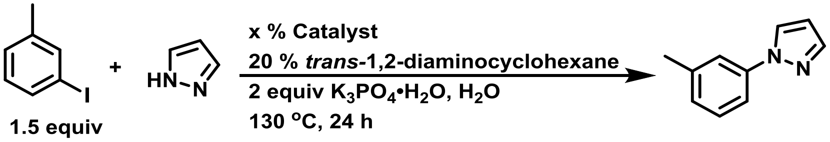
c) Some product was lost due to spill.

d) 51 % of the starting material was recovered.

At 135 °C for 21 hours with a stir bar 16 % (Entry 1) was isolated despite a minor spill of the crude mixture. The same reaction was repeated without a stir bar, which gave 22 % yield (Entry 2). Because of the spill and a 5 degrees difference between these reactions and the literature, these reactions were also performed at 130 °C. Repeating the reaction with a stir bar at 130 °C gave 11 % yield (Entry 3). Only one other spot appeared on the TLC deriving from the starting material, which was recovered in 51 % yield. Likely, the starting material unaccounted for would have been transformed into the dehalogenated compound, although it was not investigated further. The reaction was repeated without a stir bar resulting in a comparable yield of 12 % (Entry 4). Since non-deionized water contains salt impurities, the reaction was performed with water directly from the tap. This reaction resulted in 45 % yield (Entry 5). Simply using tap water improved the yield considerably indicating that the reaction could perhaps be performed with low catalyst loadings. The reaction by Teo *et al.*[98] had no proper control experiment but even so, the reactivity of the tap water is lower than that stated for the manganese catalyzed reactions.[98] The metal content in water fluctuates depending on geography so this result is not likely to be reproducible. All five reactions failed to reproduce the results of those found in the literature. The use of a magnetic stir bar did not have any influence on the reaction yield.

To complement these reactions two other experiments where performed, both without manganese, and one spiked with copper(II) chloride monohydrate. These reactions were performed in new glass vials without a stir bar. The reactions are shown in Table 9.

Table 9: Control experiment and copper catalyzed *N*-arylation.



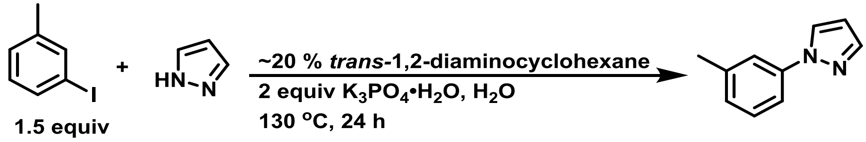
Entry[a]	Catalyst	Yield (%)[b]	Recovered 3-iodotoluene (%)
1	none	5	42
2	$CuCl_2 \cdot H_2O$ (0.1 %)	96	7

a) Using deionized water, distilled once
b) Based on pyrazole.

The experiment without catalyst gave 5 % yield (Entry 1) and this result was slightly higher than the one from a comparable reaction with the manganese catalyst (Table 8, Entry 3). On the other hand, running the reaction with 0.1 % copper(II) chloride monohydrate gave 96 % yield.

In an attempt to lower the yield of the control experiment, *trans*-1,2-diaminocyclohexane was distilled from a mixture of sodium carbonate and EDTA, while pyrazole was distilled from the same reagents. The results of the reactions are shown in Table 10.

Table 10: Purification of reagents and loading of *trans*-1,2-diaminocyclohexane ligand.



Entry[a]	3-iodotoluene	*trans*-1,2-diaminocyclohexane	Yield (%)	SM (%)
1	As purchased	22 %	2	45
2	Batch 1[b]	28 %	4	49
3	Batch 2	33 %	8	51

a) Pyrazole batch 1, *trans*-1,2-diaminecyclohexane batch 1

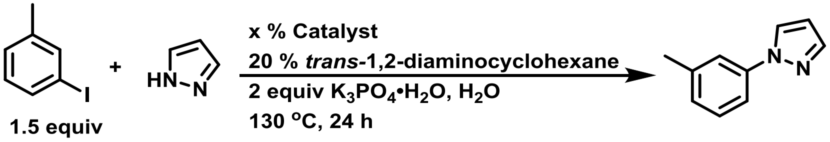
b) Discolored

The reaction without catalyst gave 2 % yield (Entry 1) indicating that trace metals in pyrazole or *trans*-1,2-diaminecyclohexane were responsible for the slightly higher, but comparable yield of the control experiment (Table 9, Entry 1). The electrophile, 3-iodotoluene was distilled under vacuum from sodium carbonate and EDTA. By accident, the substrate was left overnight in transparent glass, which resulted in the otherwise colorless transparent distillate gaining a slightly yellow discoloration. Reaction with 3-iodotoluene batch 1, resulted in 4 % yield (Entry 2). The distillation was repeated but this batch was kept carefully protected from light and remained colorless for the remaining reactions. Reaction with this batch gave 8 % yield (Entry 3). The purification of the compound seemed at first to increase the yield instead of lowering it.

Futher experiments would indicate that perhaps the increased yield was more likely a result of the slight, and unintentional, increase in the ligand. The amine ligand is somewhat difficult to weight since a single drop corresponds to several percent in loading. This is the reason for the high variation in the ligand loading. At this point, this dependence had not been observed, so the ligand loadings have been added later.

A study of the copper catalyst loading followed and the results are shown in Table 11.

Table 11: Low copper loading *N*-arylation of pyrazole.



Entry[a]	Catalyst	*trans*-1,2-diaminocyclohexane	Yield (%)[b]	SM (%)[c]
1	$CuCl_2 \cdot H_2O$ (0.01 %)	46 %	78	6
2	$CuCl_2 \cdot H_2O$ (0.001 %)	38 %	29	41

a) Pyrazole Batch 1; 3-iodotoluene Batch 2; *trans*-1,2-diaminecyclohexane batch 1

b) Based on pyrazole.

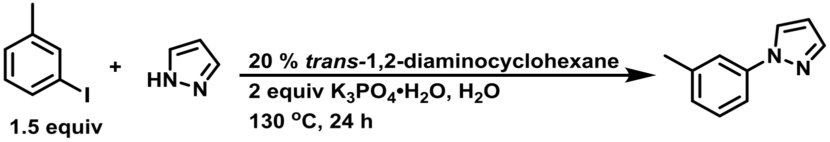
c) Recovered 3-iodotoluene.

The reaction with 0.01 % copper(II) chloride monohydrate gave 78 % yield (Entry 1). This is 18 % lower than with the 0.1 % loading experiment (Table 9, Entry 2). When lowering the loading to 0.001 % the yield dropped to 29 % (Entry 2).

The loading was not lowered further. Subsequent calculations revealed that the reaction with 10 % manganese(II) chloride tetrahydrate could potentially have a higher copper content than a reaction with a 0.0001 % copper catalyst loading.

At this point, a slight dependence on the ligand loading was suspected. Since the yield was too low to be properly mapped only two experiments were carried out. One with a high ligand loading, around 50 %, comparable to the unintentional high loading in one copper(II) chloride monohydrate experiment above (Table 12, Entry 1) and another with a loading as close to 20 % as possible. Since the lowest yields have been obtained with non-purified 3-iodotoluene (2 %, Table 10, Entry 1) this batch was selected for continued use. These reactions are shown in Table 12.

Table 12: Ligand loading in *N-arylation*



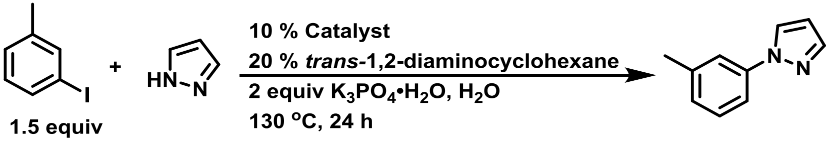
Entry[a]	*trans*-1,2-diaminocyclohexane (%)	Yield (%)[b]	SM (%)[c]
1	49	7	37
2	21	2	42
3[d]	25	3	67

a) Pyrazole Batch 1; *trans*-1,2-diaminocyclohexane batch 1; 3-iodotoluene as purchased.
b) Based on pyrazole.
c) Recovered 3-iodotoluene.
d) Solvent distilled from EDTA/Na_2CO_3/H_2O.

The reaction with 49 % ligand loading gave 7 % yield (Entry 1) and the reaction with a ligand loading of 21 % gave 2 % yield (Entry 2). These reactions were identical except for the ligand loading and showed a variation in the yield for a catalyst free control experiment. The reaction with a low ligand loading can be compared to the 22 % loading reaction (Table 10, Entry 1), as both gave 2 % yield, proving that the reaction can be controlled with a more accurate ligand loading. The third reaction was an attempt to purify the water even further by distilling deionized water from a mixture of EDTA and sodium carbonate. This reaction gave 3 % yield (Entry 3) indicating that this extra purification had no effect.

Loading the ligand into the vial first and discarding vials with too high a ligand loading helped controlling the amount of ligand used. With this simple method change, the reactions were carried out with manganese(II) chloride from different sources. These results are shown in Table 13.

Table 13: Manganese catalyzed *N*-arylations.



Entry[a]	Catalyst	Pyrazole	Yield (%)[b]	SM (%)[c]
1	$MnCl_2 \cdot 4H_2O$ (95 %)	Batch 1	8	53
2[d]	$MnCl_2$ (99 %)	Batch 1	6	53
3	$MnCl_2 \cdot 4H_2O$ (99.99 %)	As purchased	6	33
4	$MnCl_2 \cdot 4H_2O$ (99.99 %)	Batch 1	8	31

a) *trans*-1,2-diaminocyclohexane batch 1; 3-iodotoluene as purchased; 24 % *trans*-1,2-diaminocyclohexane.

b) Based on pyrazole.

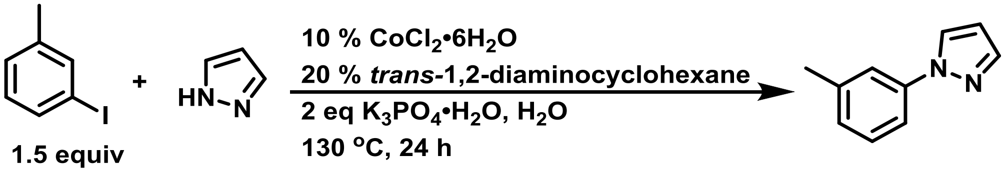
c) Recovered 3-iodotoluene

d) *23 % trans*-1,2-diaminocyclohexane.

The first reaction was performed with the 95 % pure manganese(II) chloride tetrahydrate from the first experiments (Table 8). This reaction gave 8 % yield (Entry 1), four percentage points lower than the comparable reaction before purification of the reagents (Table 8, Entry 4) but still slightly higher than the metal free reaction. Using 99 % pure manganese(II) chloride gave 6 % yield (Entry 2). Using 99.99 % pure manganese(II) chloride tetrahydrate gave 6 % and 8 % for reactions with pyrazole used without and with purification, respectively (Entry 3 and Entry 4). It would have been expected that with the increase in purity of the manganese source the yield would drop to the baseline, however, simply adding the metal gave a slight offset. Still, the reaction was not catalyzed by manganese(II) chloride, as was shown previously.

The cobalt-catalyzed reaction was tested under the same conditions, shown in Table 14.

Table 14: Cobalt catalyzed *N*-arylation



Entry[a]	Pyrazole	*trans*-1,2-diaminocyclohexane (%)	Yield (%)[b]	SM (%)[c]
1	As purchased	25	7	57
2	Batch 1	23	6	37

a) *Trans*-1,2-diaminocyclohexane batch 1; 3-iodotoluene as bought.
b) Based on pyrazole.
c) Recovered 3-iodotoluene.

The reaction with pyrazole used as bought gave 7 % yield (Entry 1) and the reaction with purified pyrazole gave 6 % yield (Entry 2).

3.2. Discussion

The manganese catalyzed reaction (Table 13, Entries 1-4) gave low yields, 6-8 %, compared to the 75 % yield reported by Teo *et al.*[98] The purity of the manganese catalyst did not affect the reaction yield, but reactions using the 99.99 % pure manganese(II) chloride tetrahydrate (Entries 3 and 4) did result in an additional decomposition of the starting material. The reactions without any catalyst (Table 13, Entries 1-3) gave comparably only traces of product, 2-7 % and indicated that manganese(II) chloride tetrahydrate does not catalyze the reaction under these conditions. When compared to the low amount of copper 0.001-0.01 % necessary to facilitate the reaction (Table 11, Entries 1 and 2) and water from the tap (Table 8, Entry 5) it seems reasonable to question the results reported by Teo *et al.*[98]

The cobalt catalyzed reaction described by Teo and Chua[100] was performed with the ligand DMEDA at 120 °C for 36 hours and gave 75 % yield. In addition, the volume of the solvent was 1.5 mL as opposed to 0.75 mL for the manganese catalyzed reaction. It was also reported that the coupling of phenyl iodide with *trans*-1,2-diaminocyclohexane for 20 hours at 120 °C gave 52 % yield compared to the optimized conditions which gave 81 % yield. Increasing the temperature by ten degrees should not reduce the yield as long as the chemicals are stable under the conditions and no side reaction is in effect. Neither seems to be the case. Using a

24 hours reaction time instead of 36 hours would lower the yield. However, the 6-7 % yield in the reactions (Table 14, Entries 1 and 2) indicate that cobalt is not an active catalyst under the conditions.

The metals, *trans*-1,2-diaminocyclohexane, potassium phosphate monohydrate and pyrazole were analyzed by ICP-MS at ALS Global for metal composition. The elements tested for were As, Ba, Cd, Co, Cr, Cu, Hg, Mo, Ni, Pb, S, Sr, Zn, Al, B, Fe, Mn, P, Si, Pd and Pt. The elements found are shown in Table 15 along with the measured purity. The main elements were of course also found, but left out in the table.

Table 15: Purity and trace metals detected.

Reagent	Purity	Elements Detected
$MnCl_2 \cdot 4H_2O$ (95 %)	90 %	Ba, **Co** (27.2 mg/kg), Hg, **Ni** (110 mg/kg), Pb
$MnCl_2$ (99 %)	92 %	Ba, Sr, Zn, Al, **Fe** (6.5 mg/kg)
$MnCl_2 \cdot 4H_2O$ (99.99 %)	97 %	Ba, Pb, **Fe** (7.84 mg/kg)
$CuCl_2 \cdot 2H_2O$ (99 %)	97 %	Pb
$CoCl_2 \cdot 6H_2O$ (99 %)	97 %	As, Pb, **Mn** (4.87 mg/kg)
DACH		Ba, Pb, Sr, Zn, **Fe** (0.0673 mg/kg)
DACH, batch 1		Pb, Zn, B, Si
$K_3PO_4 \cdot 4H_2O$		As, Ba, **Cr** (0.0851 mg/kg), Mo, Sr, B, Fe (1.24 mg/kg)
Pyrazole, batch 1		**Cr** (0.00569 mg/kg), **Ni** (0.0288 mg/kg), Zn
Pyrazole		As, Ba, Cd, Cr (0.009 mg/kg), **Cu** (0.0159 mg/kg), Hg, Pb, S, Zn, **Fe** (0.108 mg/kg), **Mn** (0.0198 mg/kg)
3-iodotoluene		-
3-iodotoluene, batch 2		-
H_2O		Ba, B
H_2O, distilled from EDTA		Ba, Pb, Zn

The difference in the reported purity and that, which is estimated based on the analysis, is not fully accounted for by the content of impurities. The difference could be explained by additional water content. This would explain why the largest difference was in the case of the hygroscopic manganese(II) chloride. Water is not an inconvenience in a reaction performed in water. Other metals, which were not detected by this analysis method, could be present, but the known cross-coupling catalyst metals are accounted for.

For the evaluation, the discussion will be limited to Co, Cu, Ni, Fe, Mn, Pd and Pt as these are associated with cross-couplings. The amounts of these elements are listed in Table 15. As for the rest of the detected elements, the highest contents detected were 25.7 mg/kg of barium, 1.31 mg/kg of lead, 1.84 mg/kg of strontium, 6.41 mg/kg of zinc, 3.05 mg/kg of aluminum, 3.30 mg/kg of boron, 2.58 mg/kg of silicium and 2.03 mg/kg of sulfur. Other elements have a content lower than 1 mg/kg or is not found and have a detection limit of 1 mg/kg or lower.

The metal content for each reaction was calculated using the following method: The metal content, or detection limit when no metal was detected, was used to calculate the content for the mass of each reagent used in the reaction. This content was summed over each reagent present in the reaction to get the total maximum metal loading.

The manganese and cobalt content is summarized in Table 16.

Table 16: Manganese and cobalt content of the reactions.

Reaction with	Manganese Content	Cobalt Content	Yield
Manganese (95 %)	9.0 %	0.0009 %	8 %
Manganese (99 %)	9.6 %	0.0001 %	6 %
Manganse (99.99 %)	9.1 %	0.0002 %	6-8 %
Cobalt	0.0003 %	9.7 %	6-7 %
Copper (0.1 % loading)	0.00008 %	0.000009 %	96 %
Copper (other loadings)	0.00009 %	0.000008 %	29-78 %
Remaining Reactions	0.00009 %	0.000008 %	2-8 %

This presentation of the experimental results shows that there is no correlation between the amounts manganese or cobalt and the reactivity.

Palladium and platinum were not detected and in general had low detection limits. For palladium, a 0.00003 % content would be maximum while it was 10 times lower for platinum. Iron was present in small amounts in all the reactions, due to its presence in potassium phosphate tribasic monohydrate, resulting in a 0.0012 % iron content in the reactions where there was no catalyst present. In the reactions with catalysts present this number went up to 0.0015 %, either because of its content in two of the manganese species or because of the <5 mg/kg detection limits for the remaining metals.

Nickel was detected in 110 mg/kg in manganese(II) chloride tetrahydrate (95 %) resulting in a 0.004 % maximum content for these reactions. In cobalt(II) chloride hexahydrate the detection limit of nickel was 200 mg/kg resulting in a maximum of 0.008 %. For reactions with other manganese catalyst sources the content was twenty times lower and for reactions without any metal catalyst, the content was fifty times lower.

The copper contents of the reactions are shown in Table 17.

Table 17: Copper content of the reactions.

Reaction	Copper Content	Yield
Reaction with 0.1 % copper	0.097 %	96 %
Reaction with 0.01 % copper	0.0097 %	78 %
Reaction with 0.001 % copper	0.0010 %	29 %
Manganese catalyzed	0.00043-0.00065 %	6-8 %
Cobalt catalyzed	0.00005 %	6-7 %
Metal free	0.00003 %	2-8 %

The reactions with 0.1 and 0.01 % copper(II) chloride dihydrate led to 96 % and 78 % yield, respectively. A hypothetical copper impurity in manganese(II) chloride tetrahydrate and cobalt(II) chloride hexahydrate can be calculated. For manganese(II) chloride tetrahydrate it is 311-3118 mg/kg, or 0.03-0.3 %. For cobalt(II) chloride hexahydrate an impurity of 260-2600 mg/kg, or 0.03-0.3 %, would be needed. If the impurity is calculated as copper(II) chloride dihydrate the necessary content is 0.08-0.8 % for manganese(II) chloride tetrahydrate or 0.07-0.7 % in cobalt(II) chloride tetrahydrate.

These numbers indicate that running the reaction with a 98 % pure metal source as reported in the literature is not sufficient to ensure that this reaction is not catalyzed by trace metals. It does not explain how the experiment performed with

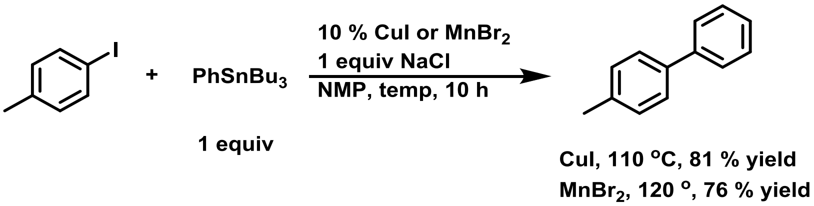
99.99 % pure manganese(II) chloride tetrahydrate gave 64 % yield as reported by Teo *et al.*[98] This reaction, like the optimization reported could be explained by copper contaminations of the water source. However, that explanation does not hold with the cobalt catalyzed reaction[100] since the control experiment here gave no product.

3.3. Conclusion

It was not possible to reproduce the manganese catalyzed cross-coupling results reported in 2009 by Teo *et al.*[98] The reaction gives a good yield with low loadings of copper which is most likely the true catalyst for the transformation. The loadings required are not as low as the similar reaction in toluene but can still cause complications for anyone wishing to examine the cross-coupling potential of other metal catalysts. In fact, it was not possible to reproduce the control experiments to achieve no conversion, like those reported in the cobalt[100] and iron[101] catalyzed reactions under similar conditions,[100,108] despite using new glassware, no magnet and purifying most of the chemicals including the solvent.

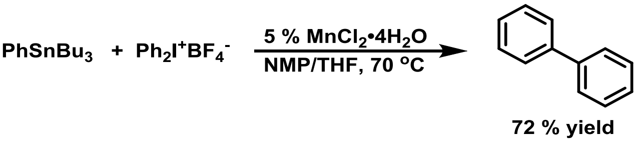
4. Manganese Catalyzed Stille Cross-Couplings

In 1997 Kang *et al.*[109] reported a successful manganese and copper catalyzed cross-coupling of aryl and β-styryl iodides with various organostannanes. The catalyst was 10 % manganese(II) bromide or 10 % copper(I) iodide with 1 equivalent of sodium chloride or potassium chloride as an additive in NMP or DMF with the temperature ranging from 90 to 120 ^{0}C degrees, depending on the substrate. Conditions are illustrated for the coupling between tolyl iodide and phenyltributylstannane in Scheme 39.



Scheme 39: Manganese catalyzed Stille cross-coupling of tolyl iodide by Kang *et al.*[109]

In 1998 Kang and co-workers[110] expanded the scope of the manganese catalyzed cross-coupling by using a hypervalent iodonium salt as an electrophile to both lower the reaction temperature and to allow the use of carbon monoxide in a three component carbonylative Stille cross-coupling. The electrophiles were aryl, β-styryl or 4-anisole phenyliodonium tetrafluoroborate. The conditions for the reactions were 5 % manganese(II) chloride tetrahydrate in 2:1 THF/NMP, at 70 ^{0}C or 60 ^{0}C, with or without 1 atm carbon monoxide. The conditions for the non-carbonylative coupling of diphenyliodonium tetrafluoroborate and phenyltributylstannane are shown in Scheme 40.

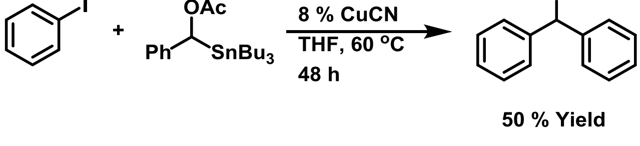


Scheme 40: Manganese catalyzed Stille cross-coupling using hypervalent iodonium electrophile by Kang and co-workers.[110]

A literature search revealed no other examples of manganese catalyzed Stille cross-couplings.

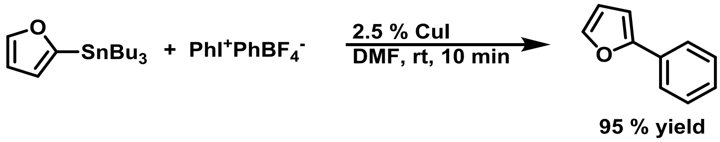
Kang *et al.*[109] reported that the reactions with aryl bromides and triflates did not result in any product. Aryl iodides are generally considered better electrophiles in cross-coupling reactions compared to bromides, chlorides and sulfonates due to their higher reactivity in the oxidative addition, which is often the rate-determining step. Although the oxidative addition step is common for all cross-couplings, the mechanism is dependent on the electrophile. For this reason, the following comparison of other metals catalyzing the Stille reaction will be restricted to couplings with aryl iodides. The examples where hypervalent iodonium electrophiles are used will be also presented for a more complete picture.

The Stille cross-couplings with aryl halide electrophiles are mainly performed by palladium catalysis but examples were also found, where copper and nickel are catalyzing the reaction. Initially copper(I) iodide was found to have a positive effect on the palladium catalyzed cross-coupling. In palladium catalyzed Stille cross-couplings in ethereal solvents this effect was attributed to copper acting as a phosphine ligand scavenger. Here the transmetalation required the phosphine ligand to leave to facilitate an associative transmetalation.[111] In DMF and NMP the activity of the reaction is improved. This improvement in activity has been attributed to a preliminary transmetalation between the tin nucleophile and the copper additive.[112] In both THF and NMP the optimal amount of copper(I) additive appears to be 2:1 with respect to the palladium catalyst. Using copper(I) iodide without palladium in NMP at 100 °C gave 5 % conversion and 27 % yield when reacted at 140 °C.[113] Finally, in 1995 Falck *et al.*[114] reported the copper catalyzed Stille cross-coupling using 8 % copper(I) cyanide in THF at 60 °C as shown in Scheme 41.



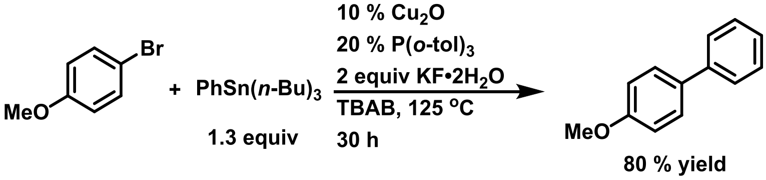
Scheme 41: Copper catalyzed Stille cross-coupling without ligand by Falck *et al.*[114]

Other copper species, such as copper(I) iodide, and the rhodium complex tris(triphenylphosphine)rhodium(I) chloride were also reported to catalyze the coupling, although to a somewhat lower extent. No other reports on the catalytic potential of rhodium on aryl halide electrophiles was found in the literature. However, rhodium has been used as a catalyst in the coupling of allylstannanes as early as 1977 when Kosugi *et al.*[115] reported the coupling with an acid chloride electrophile. The second copper catalyzed Stille cross-coupling was reported by Kang and co-workers[116] in 1996. Here hypervalent aryl iodides were used in DMF at room temperature to perform the coupling in just 10 minutes with a 2.5 % copper(I) iodide loading and the reaction was also expanded to include the carbonylative coupling. The conditions are shown in Scheme 42.



Scheme 42: Copper catalyzed Stille cross-coupling by Kang and co-workers.[116]

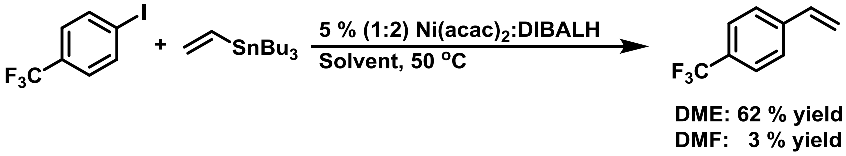
The third paper from 2006, by Li *et al.*[117] on the copper catalyzed Stille cross-coupling employed copper(I) oxide nanoparticles as the catalyst and ionic liquids as the solvent. One experiment was performed with regular copper(I) oxide and the conditions for the reaction are shown in Scheme 43.



Scheme 43: Copper catalyzed Stille cross-coupling by Li *et al.*[117]

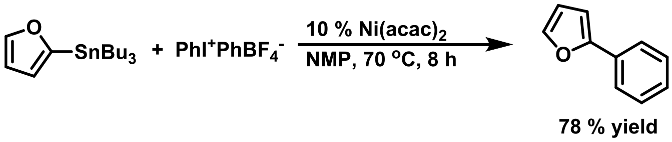
The reaction with copper(I) oxide nanoparticles was also successful with iodides and chlorides. Since the optimization showed that nanoparticles only perform slightly better than regular copper(I) oxide (90 % vs 98 % yield) it is reasonable to expect that copper(I) oxide would catalyze the reaction for aryl iodides as well.

A literature search revealed three papers with nickel catalyzed Stille reactions. In 1997 Hiyama and co-workers[118] added diisobutyl aluminum hydride (DIBALH) to a mixture of nickel(II) acetylacetonate, triphenylphosphine and an organostannane together with an aryl bromide or chloride. The relative quantities of DIBALH, precatalyst and ligand indicated the active catalyst was tetra(triphenylphosphine) nickel. In 1998 Hiyama and co-workers[119] expanded this method. Interestingly, a phosphine ligand was not used in the reaction, which gave moderate yields with 4-trifluoromethylphenyl iodide as the electrophile in DME as the solvent. The reaction conditions are shown in Scheme 44.



Scheme 44: Nickel catalyzed Stille cross-coupling without ligand by Hiyama *et al.*[119]

In 1999 Kang and co-workers[120] developed the ligand free nickel cross-coupling using nickel(II) acetylacetonate in NMP at 70 °C to couple hypervalent iodonium electrophiles with organostannanes. The conditions are shown in Scheme 45.



Scheme 45: Nickel catalyzed Stille cross-coupling using hypervalent iodonium electrophile by Kang and co-workers.[120]

The scope of the reaction overlaps to some extend with the previously developed manganese cross-coupling, where the hypervalent iodonium electrophile was used. The reaction is shown in Scheme 40 and the comparison between the two reactions is shown in Table 18.

Table 18: Comparison of yields for the manganese and nickel catalyzed Stille cross-coupling[110,120]

$$R^1SnBu_3 + R^2I^+PhX^- \xrightarrow{Ni(acac)_2 \text{ or } MnCl_2 \bullet 4H_2O} R^1\text{-}R^2$$

		R^1			
Catalyst	**R^2**	Thionyl	Furyl	Styryl	Ethynylbenzene
$MnCl_2 \bullet 4H_2O$	Ph	80 %	84 %	67 %	72 %
$Ni(acac)_2$	Ph	79 %	78 %	82 %	80 %
$MnCl_2 \bullet 4H_2O$	4-MeOPh	71 %	61 %		
$Ni(acac)_2$	4-MeOPh	77 %	54 %		

The yields for the two reactions are comparable, and show that the hypervalent iodonium moiety is a good electrophile both with the nickel and the manganese catalyst. The coupling with a hypervalent iodonium electrophile can be performed by a palladium catalyst at room temperature in 5:1 acetonitrile/water.[121]

Amongst the non-palladium catalyzed Stille cross-couplings nickel have the broadest scope in the literature.[118–120] Nevertheless, while nickel is cheaper than palladium, it is toxic.[122] Between copper and manganese, copper offers the lower temperature with a longer reaction time compared to manganese, while the latter have the larger scope when aryl halides are used as electrophiles.[109,110,116] At higher temperatures the copper catalyzed reaction in ionic solvents can couple aryl bromides and chlorides in addition to aryl iodides.[117]

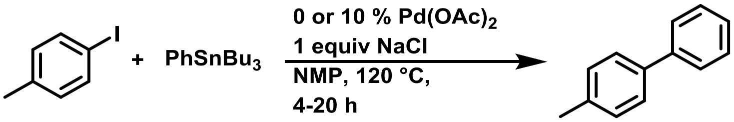
The palladium catalyzed Stille cross-coupling reaction can be performed under various atmospheres. Using nitrogen or argon to avoid air is recommended to reduce the amount of the homocoupling byproduct. However, reaction procedures that require an inert atmosphere appear to be about equal in number to those who do not. The reactions that require an inert atmosphere often use a palladium complex with phosphine ligands.[123] This is not surprising since phosphine ligands are air sensitive and are likely the primary reason for using the inert conditions.[3] As such, the palladium catalyzed reactions with phosphine ligands referred to in this chapter have been performed under inert conditions.[111–113] For the reactions with hypervalent iodonium electrophiles the nickel catalyzed[120] version was performed under inert atmosphere, while the manganese[110], copper[116] and palladium[121] catalyzed procedure were not. The nickel catalyzed reactions using a DIBALH generated catalyst[118,119] also needed an inert atmosphere, which is a general requirement for nickel(0) catalyzed reactions.[124] The copper catalyzed Stille reaction by Falck *et al.*[114] was performed in an inert atmosphere while the copper catalyzed reactions by Kang *et al.*[109] and Li *et al.*[117] were not. The manganese catalyzed Stille cross-coupling[109] reaction was not performed in an inert atmosphere.[109]

That the Stille cross-coupling reaction can be catalyzed with manganese is an interesting innovation, and suggests that a number of other cross-couplings may be performed with manganese as well. However, there are a few things worth noticing when comparing the literature data. The manganese reaction by Kang *et al.*[109] share conditions and scope with a copper(I) iodide catalyzed reaction. Copper catalyzed Stille cross-couplings almost uniformly have special requirements with regards to the nucleophile, which are not met here. The other examples where aryl halides can be coupled with traditional aryltrialkyl tin species are when ionic liquids are used at higher temperature.[117] The manganese catalyzed coupling of hypervalent iodonium electrophiles[110] has the same scope as the nickel catalyzed cross-coupling.[120] Among these reactions, four are reported from 1996 to 1999 which only work with the most reactive of the aryl halides and a share one common author. A paranoid chemist could worry that a single bottle of NMP with a metal impurity was the cause for all these results.

4.1. Results

An earlier attempt to validate the manganese catalyzed Stille cross-coupling by Kang *et al.*[109] has been performed by Sølvhøj[125] without success. The reaction was reported[125] with 4-iodotoluene and tributylphenylstannane using a palladium catalyst, which gave a fair amount of conversion, followed by two reactions with manganese(II) bromide as the catalyst that gave no product. Similarly, the reaction with copper(I) iodide did not result in any yield.[125] Since only these conditions for the manganese catalyzed Stille cross-coupling were found in the literature, they would have to serve as the entry point for a new study of this reaction. The reactions were performed with the intention of expanding the examination with different metals as compared to the previous study and test the influence of palladium contamination.

Before the work was started, the conditions were tested both with 10 % palladium and without any catalyst. These reactions were performed to ease the further work such as identifying problems in the setup. Besides identification of TLC spots and a solvent system for column chromatography, the GCMS and ^{1}H NMR peaks for products and side products could also be noted for future reference. The reaction without a catalyst was a simple control experiment. A positive result would indicate either that the reaction could run without a catalyst or that other problems, such as trace metal impurities were interfering with results. New glassware and stir bars were used for each reaction. The conditions are shown in Scheme 46.



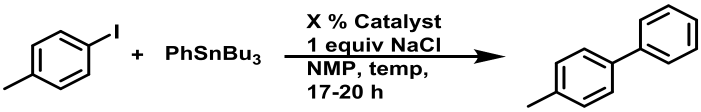
Scheme 46: Stille cross-coupling with palladium catalyst and the control experiment.

The reaction with the palladium catalyst was performed over 4 hours, since only quantitative information was needed, and the conditions were not optimized for this catalyst. The workup was performed with saturated sodium carbonate and diethyl ether extraction, followed by column chromatography in pentane. The product, biphenyl and bitolyl homocouplings were isolated as one compound. ^{1}H NMR and GCMS data indicated that 4-methylbiphenyl was present in around 21 % yield. The reaction without catalyst was left for 20 hours to increase the yield from a possible background reaction. Following workup, the crude was examined by GCMS and indicated no formation of neither product nor biphenyl homocoupling side product. The sample contained several compounds, the masses of which corresponded to the starting material, various tin species and octane. ^{1}H NMR of the relevant fractions from column chromatography showed peaks corresponding to those found in the literature for 4-iodotoluene and tributylphenylstannane.[126,127] Overall, these experiments indicated that there was no problem with the reaction conditions, experimental setup, reactants, workup or identification of the product.

Next, the validation experiments were performed. Manganese(II) bromide was used as a catalyst with conditions similar to those used by Kang and co-workers[109] for the coupling with 4-iodotoluene and phenyltributylstannane. Copper(I) iodide was also used as a catalyst under the conditions reported for the reaction.

Reactions with nickel(II) chloride, cobalt(II) chloride hexahydrate were also performed as shown in Table 19.

Table 19: Catalyst screening for the Stille cross-coupling.



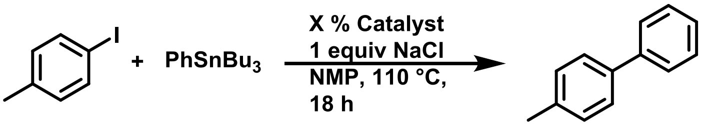
Entry	Catalyst and Loading	Temperature (°C)	GCMS Conversion
1	10 % $MnBr_2$	120	< 1 %
2	10 % CuI	110	none
3	10 % $MnBr_2$	110	none
4	10 % $NiCl_2$	120	none
5	10 % $CoCl_2 \cdot 6H_2O$	120	none

The crude from the reaction with 10 % manganese(II) bromide (Entry 1) gave a trace peak of the product on the GCMS. The relative area compared to the starting material indicated less than 1 % conversion. When the reaction did not work, the literature was consulted again and the only difference between the work by Kang *et al.*[109] and the reaction described above was that the workup was performed with saturated potassium fluoride instead of saturated sodium carbonate. Fluoride ions are known to react with tributyltin chloride to form the more insoluble tributyltin fluoride and thus facilitate easy workup.[128] Saturated potassium fluoride has also been used as an additive in the palladium catalyzed Stille cross-coupling to improve the yield.[129] Because the workup is performed after the reaction have cooled down, the modification is unlikely to result in any change in the reaction yield. The remaining reactions was worked up with saturated potassium fluoride. The reaction using 10 % CuI as the catalyst was performed at 110 ^{o}C (Entry 2) and the GCMS of the crude did not show any conversion. Manganese(II) bromide was used again at 110 ^{o}C (Entry 3) and the GCMS was no longer showing the trace of the product. Finally, nickel(II) chloride and cobalt(II) chloride hexahydrate were used in reactions at 120 ^{o}C (Entries 4 and 5). The GCMS spectra for the crudes of these reactions did not show any conversions.

Problems with small quantities of palladium have previously resulted in false positives for other cross-coupling reactions, such as the iron catalyzed Buchwald-

Hartwig cross-coupling described in the previous chapter. For this reason, experiments were performed to test the resistance of the reactions to palladium impurities. Since the reaction with palladium(II) acetate (Scheme 46) have already been shown to yield some product, this reaction was selected for a gradual reduction of palladium catalyst to simulate the influence of impurities on the reaction yield. The reaction was performed by making a stock solution of palladium(II) acetate in NMP that could be additionally diluted to reach the catalyst loadings, which could not be easily done by using a scale. The reactions are shown in Table 20.

Table 20: Screening for resistance to palladium contamination.



Entry	Catalyst and Loading	Yield[a]
1	10 % $Pd(OAc)_2$	52 %
2	2.4 % $Pd(OAc)_2$	41 %
3	0.3 % $Pd(OAc)_2$	35 %
4	0.03 % $Pd(OAc)_2$	42 %
5	0.003 % $Pd(OAc)_2$	42 %
6	0.0004 % $Pd(OAc)_2$	none
7	8 % $Pd(OAc)_2$, 10 % CuI	44 %

a) Based on the GC composition of the isolated mixture of product and homocouplings.

After the workup of each reaction, the crude was purified by column chromatography in pentane, which gave a mixture of the cross-coupling product, 1,1’-biphenyl and 4,4’-dimethyl-1,1’-biphenyl. Estimation of the product was based on the relative areas of the GCMS peaks. The reaction time was 18 hours for all reactions and the temperature was set to 110 °C, although the corresponding manganese(II) bromide catalyzed reaction by Kang and co-workers[109] was performed for 10 hours at 120 °C. The purpose of the reaction was to observe how low quantities of palladium would be able to catalyze the reaction and to get an idea of how rapidly the yield would drop with lower amounts of catalyst. For this purpose the longer reaction time would not interfere, while the reduced temperature corresponding to the reaction with copper(I) iodide, might result in a lower reactivity. The first reaction was performed with 10 % palladium(II) acetate (Table 20, Entry 1) and led to 52 % yield, which was more than the initial reaction, which was run for 4 hours at 120 ^{0}C (Scheme 46) and only yielded 21 % product. This increase in the reaction yield was most likely due to the longer reaction time. A 52 % yield confirmed that the reaction worked at 110 ^{0}C, and that palladium(II) acetate would suffice as an impurity at this temperature. The loading was reduced to 2.4 % (Entry 2) and the reaction gave 41 % yield. The reaction with a catalyst loading of 0.3 % (Entry 3) gave 35 % yield while reactions with 0.03 % and 0.003 % palladium(II) acetate (Entries 4 and 5) both resulted in 42 %. With a catalyst loading at 0.0004 % (Entry 6) the product and the homocoupling byproduct were no longer present, but the starting material was. As discussed previously, copper(I) iodide have been found to have a positive effect on the palladium catalyzed cross-coupling. To test whether it could be a dual catalytic effect that boosted the yield of the reaction, it was performed with 8 % palladium(II) acetate and 10 % copper(I) iodide (Entry 7). The resulting yield of 44 % was not significantly higher compared to the reactions with 10 % and 2.4 % palladium(II) acetate, where 52 % and 41 % yield was obtained, respectively. As a result, this reaction was not repeated with a lower catalyst loading. Gold has also been reported to be a co-catalyst.[130] The reactions with palladium and gold were unfortunately not examined under these conditions.

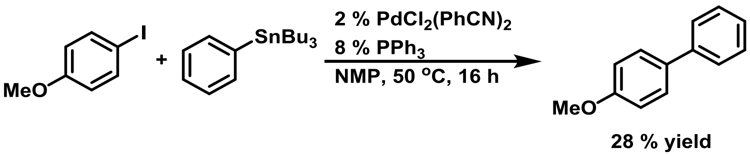
4.2. Discussion

The procedure for the manganese and copper catalyzed Stille cross-coupling calls for the slow addition of the organotin species over an hour. When the nucleophile was added in one portion the yield decreased significantly, while the yield of the homocoupling product increased.[109] The slow addition is generally recommended to avoid formation of the homocoupling product.[123] However, this precaution is not always taken. The previously mentioned palladium catalyzed Stille cross-coupling by Farina *et al.*[113] simply added the organotin compound before heating the reaction. All reactions carried out in this study were performed with a 1 hour addition period for consistency.

In the examples of the nickel catalyzed ligand free Stille cross-couplings presented earlier in this chapter, all have been carried out under an argon/nitrogen atmosphere.[118–120] Since this is typically required for nickel catalyzed reactions, it was not unexpected that no reaction was observed under a non-inert atmosphere. All reactions have been performed for 17 hours or longer, which was more than the 10 hours reaction time, reported in the original procedure.[109]

It was not possible to reproduce the reactions by Kang and co-workers[109] using manganese(II) bromide or copper(I) iodide. Furthermore, cobalt(II) chloride hexahydrate or nickel(II) chloride did not catalyze the reaction under the conditions. The three nickel catalyzed Stille reaction procedures referenced above all used nickel(II) acetylacetate as the precatalyst under an inert atmosphere.[118–120] The two reactions using traditional aryl halide electrophiles needed diisobutylaluminium hydride to activate nickel. The fact that the reactions did not give any product under these conditions is not surprising and does not rule out that the reaction could be performed in the presence of a proper tuned nickel catalyst. Nickel(II) is the most common oxidation state[131], so if nickel impurities have been responsible for the results by Kang and co-workers,[109] the reaction with nickel(II) chloride would have been expected to give at least a trace yield.

The results obtained with palladium(II) acetate as catalyst, as shown in Table 20, can be compared with results from the literature. Farina *et al.*[113] have performed the reaction with a palladium phosphine complex as the catalyst at 50 °C using 2 % catalyst, which gave 28 % yield and 69 % of the starting material, using 4-iodoanisole as the electrophile. The reaction is shown in Scheme 47.



Scheme 47: Palladium catalyzed cross-coupling with phosphine ligand by Farina et al.[113]

An electron rich electrophile is a worse substrate for the oxidative addition than an electron poor electrophile since the oxidative addition is often the rate limiting step in the palladium catalytic cycle this means electron poor electrophiles often perform better in cross-couplings.[23] However, for the palladium catalyzed Stille cross-coupling with phosphine ligands, and in particular the triphenylphosphine ligand, the rate limiting step is likely the transmetalation step.[132] Therefore, for the reactions described above with 4-iodoanisole and 4-iodotoluene should be sufficient to illustrate the difference in activity for the palladium catalyst and the phosphine ligand tuned palladium catalysts. With four triphenylphosphines for the precatalyst, the temperature can be lowered by 60 ^{o}C and results in only a 13 % lowering of the yield. Note that this reaction is selected for comparison based on the solvent, the substrates, and not to achieve a high yield for an optimized reaction.

To further evaluate these results, all electrophiles, nucleophiles, additives, catalysts and solvents from the metal catalyzed Stille cross-coupling were sent for ICP-MS elemental analysis at ALS Global. A total of 21 metals and semimetals were tested for. Based on their metal content the purity of the reagents was estimated assuming that all metals detected were in the oxidation state with the correct ligands shown in Table 21. The detection limits of nickel in cobalt(II) chloride hexahydrate was 200 mg/kg and the detection limit for silicon and sulfur were up to 100 mg/kg. For copper in the case of manganese(II) bromide the detection limit was 20 mg/kg and for aluminum and phosphor the detection limits were up to 10 mg/kg. The detection limit for iron was up to 5 mg/kg, while boron had a detection limit up to 2 mg/kg. The detection limit for all other elements tested, were 1 mg/kg or less. Elements that were detected are reported in Table 21.

Table 21: Overview of impurities in compounds

Compound	Purity (%)	Impurities[a]
Copper(I) Iodide	97	Hg, Pb
Manganese (II) Bromide	85	Ba (2.75 mg/kg) , Cd, Co (8.64 mg/kg) , Cr (3.30 mg/kg) , Mo, Pb (1.29 mg/kg) , Zn (19.3 mg/kg) , Al (19.3 mg/kg), Fe (470 mg/kg), P (17.6 mg/kg)
Cobalt(II) Chloride Hexahydrate	96	Pb, Mn (4.44 mg/kg)
Nickel(II) Chloride	94	Cr, Pb
Palladium(II) Acetate	98	Pt (7.70 mg/kg)
4-iodotoluene		Cd, Cr, Cu, Hg, Pb, Sr, Zn
Phenyltributylstannane		As
N-Methyl-2-pyrrolidone		Ba
Sodium Chloride		Pb

a) when amount not noted means less than 1 mg/kg

Among these impurities only the cobalt, copper, nickel, palladium, platinum, iron, and manganese contents were evaluated for the reactions. Recalculation of the metal content for the reactions was done by adding the metal content of the starting materials, additives, catalysts and solvents together, based on the assumption that each compound contained the borderline value of a metal impurity to the detection limit. Disregarding the metal catalyst content itself, the impurities never exceeded the values in Table 22.

Table 22: Maximal metal impurities reported in equivalents.

Metal Impurity	Loading (mol %)
Palladium	0.0004
Nickel	0.0006
Cobalt	0.0004
Manganese	0.0004
Platinum	0.0004
Iron	0.03
Copper	0.001

The high platinum content was due to the impurity in palladium(II) acetate. For reactions without this catalyst the maximum dropped to 0.00002 %. Likewise the relative high iron and copper content was a consequence of their high content in manganese(II) bromide. For other reactions the amount of iron and copper never exceeded 0.004 % and 0.0004 %, respectively.

For the reaction with 0.003 % palladium(II) acetate (Table 20, Entry 5) the palladium content including impurities was calculated to the same value. The iron content was calculated to be slightly higher at 0.004 %. The content of nickel, manganese and copper was smaller by a factor of 10, and the content of cobalt and platinum was smaller by a factor of 100 and 200 times, respectively.

When only 0.0003 % palladium(II) acetate was used (Entry 6), the metal impurities (or rather the detection limits) of phenyl tributylstannane started to affect the calculated metal content of the reaction. The detection limits in NMP were at least 50 times lower than in the organostannane and were therefore not contributing much to the final impurity estimation, despite the use of 13 times as much by mass. The palladium content was estimated to be 0.0006 % and the iron content to be 0.003 %. The nickel, manganese and copper content was 0.0003-0.0004 % while cobalt and platinum were around 10 and 40 times lower. By comparison the failed reactions with manganese(II) bromide (Table 19, entry 1 and 3), copper(I) iodide (Entry 2), nickel(II) chloride (entry 4) and cobalt(II) chloride hexahydrate (Entry 5) contained no more than 0.00034 % palladium. This number is solely based on the respective detection limits for palladium in the reagents of the reaction, and primarily based on the 1 mg/kg detection limit of palladium in phenyl tributylstannane. The palladium loading for these reactions was lower than the amount needed and the reaction would only have been possible if the metals themselves had catalytic effect or enhanced the catalytic effect of palladium.

The reaction with 10 % copper(I) iodide (Table 19, Entry 2) is carried out under the same conditions as those described by Kang *et al.*[109], previously shown in Scheme 39, who reports a 81 % yield. Kang *et al* [109] used two batches of copper(I) iodide, one 99.999 % from Aldrich Chem. Co. and the second 98 % from Janssen Chimica. Unfortunately, it is not clear which reactions have been performed with which copper(I) iodide or whether they have tried several reactions with the same copper source with similar results. The metal and additive optimization by Kang *et al.*[109] shows that when the additive is sodium chloride or potassium chloride, copper(I) iodide and manganese(II) bromide is reported to have comparable high yields around 85 %. Lithium chloride also performs well with copper(I) chloride with a 80 % yield. Manganese(II) bromide and lithium chloride gave only 10 % yield while the additives potassium fluoride and cesium fluoride gave yields between zero and 40 % with both metals. Furthermore, the cross-coupling product was reported in 20-50 % yield in these reactions. Kang *et al.*[109] also reported that the reactions were performed with manganese(II) chloride tetrahydrate with a lower yield and manganese(II) iodide with no coupling product.

The difference in yields from Table 19 and those reported by Kang *et al.*[109] are around 30 % over a range of loadings of 0.003 % to 10 % palladium(II) acetate. While the reported results could not be replicated, an explanation based solely on trace palladium impurities is insufficient to account for these high yields. Also if metal impurities were to be part of the explanation, it would need to be a contamination of several of the reagents or solvents used in the experiments, since no single parameter can be deduced to account for the high yields.

While performing the Stille cross-coupling using hypervalent iodonium electrophiles Kang and co-workers first used copper(I) iodide to perform the coupling at room temperature in 10 minutes[116] and palladium(II) chloride in 30-90 minutes.[121] When nickel(II) acetylacetonate[120] or manganese(II) chloride tetrahydrate[110] was used, the temperature was 70 ^{o}C and the reaction time was up to 8 hours and 15 hours, respectively. With this electrophile, copper and manganese had different reactivities. When changing to aryl iodides the copper and manganese catalyzed reactions share reaction times and temperatures within 10 ^{o}C and have almost comparable yields.[109] These results cannot be directly compared since reactions with different electrophiles might have different mechanisms even if they both go through the oxidative addition step. However, the former reaction could be an indication that the transmetalation and reductive elimination steps for a manganese catalyzed reaction could run at 70 ^{o}C, meaning that only the oxidative addition of aryl halides needs the higher temperature.

The copper catalyzed Stille reaction with other electrophiles had an oxygen on the carbon alpha to tin and in all but one case a heteroatom substituent at the 2-position facilitating chelation.[130] This indicated that the mechanism for this reaction is different, which is also supported by the much lower reaction temperature.[114] In the copper mediated coupling with 1.5 equivalent of copper(I) thiophene-2-carboxylate[133] in NMP at 0 ^{o}C to room temperature, aryl iodides were found to be poor substrates, even though the electrophiles for the failed reactions were not reported. Only 2-iodonitrobenzene reacted and gave 73 %, while the reaction with 4-iodonitrobenzene failed. Under these conditions, the reaction between styryl tributylstannane and β-iodostyrene gave 89 % product in 5 minutes at 0 ^{o}C. Compared to the same reaction that afforded 90 % and 81 % of product, respectively, after 12 and 15 hours with copper(I) iodide and manganese(II) bromide at 120 ^{o}C.[109] This could be attributed to copper(I) thiophene-2-carboxylate somewhat resembling the proposed intermediate of copper after transmetalation with a chelating stannane.[114]

When comparing the results in the literature it is noteworthy that for the conditions involving these reactions the metal chosen for the reactions is interchangeable with another metal that is not well explored either.

4.3. Conclusion

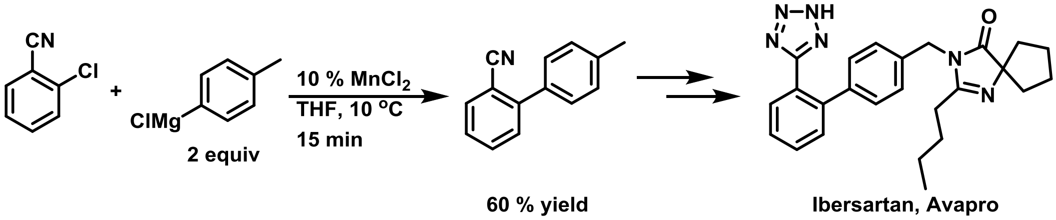
The manganese catalyzed Stille reaction is underdeveloped and only presented by two examples in the literature. These reactions have similar conditions and reactivity to that of a copper catalyzed Stille and, in the case of the reaction with hypervalent iodonium nucleophile, a nickel catalyst.

Under the conditions reported it was not possible to reproduce the reactions with aryl halide nucleophiles with neither the manganese nor the copper catalyst. However, it was shown that a 42 % yield could be achieved with a 0.003 % palladium(II) acetate loading, indicating that care should be taken whenever such reactions are examined.

5. Manganese Catalyzed Kumada Cross-Couplings

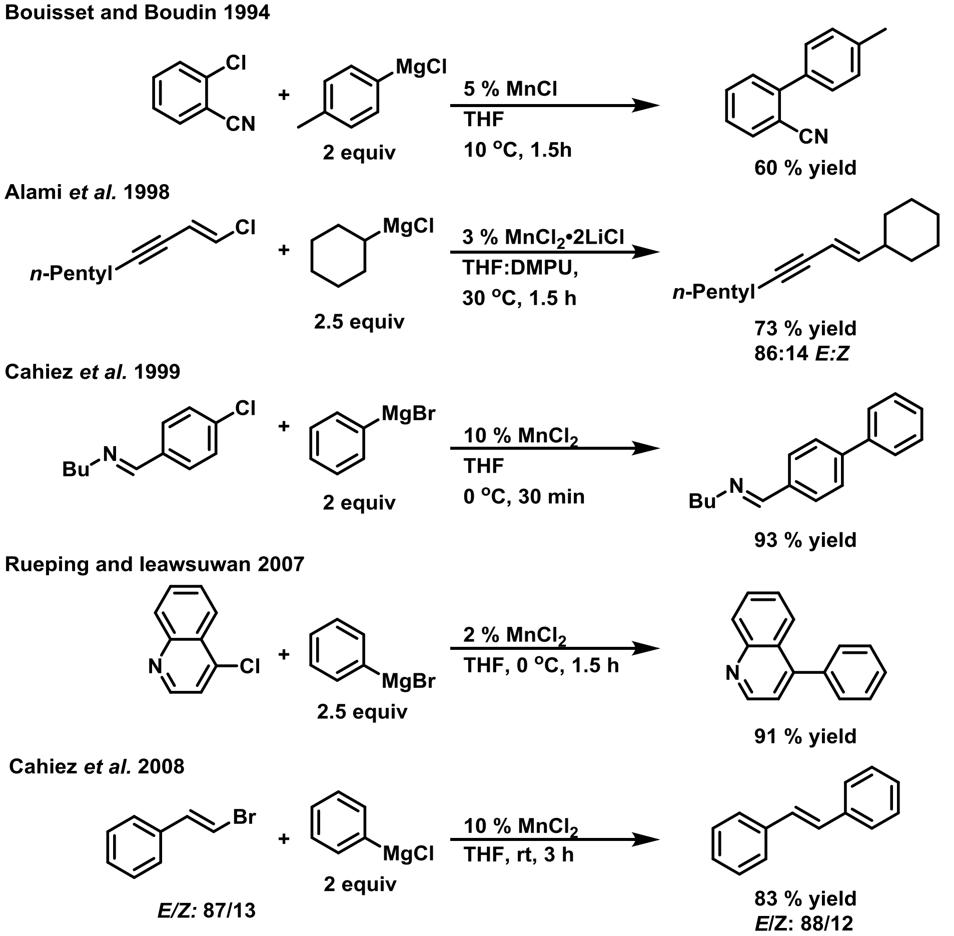
Manganese has been known as a substitute for magnesium in Grignard reagents and that these organomanganese halides compounds are softer nucleophiles than the corresponding Grignard reagents. The reactivity of manganese compounds as nucleophiles towards ketones is somewhere between magnesium and zinc. One way of preparing the organomanganese halide is by reacting manganese(II) choride bis(lithium chloride) with a Grignard reagent. One advantage of this reagent is the tolerance of additional functional groups such as esters, nitriles and amides.[134,135]

The literature presents a few examples of manganese catalyzed cross coupling with organomagnesium chlorides as shown in Scheme 49. The first is by Bouisset and Boudin[136] in 1994 who synthesized 4-methyl-2'-cyanobiphenyl with 5 to 100 % manganese(II) chloride from 2-cyanophenyl halide and tolylmagnesium chloride.[136] The product is important as an intermediate in the synthesis of Ibersartan which is an antihypertensive drug.[137]



Scheme 48: Manganese catalyzed cross-coupling by Bouisset and Boudin[136] towards an intermediate in the formation of Ibersartan.[138]

In 1998 Alami *et al.*[139] reported a manganese catalyzed coupling of various chloro-but-1-en-3-ynes with alkyl and aryl Grignard reagents. In 1999 Cahiez *et al.*[140] expanded the scope of the reaction patented by Bouisset and Boudin.[136] The electrophiles were, in addition to 2-benzonitriles, *N-tert*-butyl phenylmethanimine derivatives and 1-chloro-2-styrylbenzene. Bromide, chloride, fluoride and methoxy derivatives of phenylmethanimines gave comparable yield under these conditions. In 2004 Cahiez and coworkers[141] further expanded the scope, to include 2-aryl ketones when reacting with phenylmagnesium chloride. However, for using other nucleophiles it was necessary to use stoichiometric manganese(II) chloride bis(lithium chloride) stirred with the nucleophile before adding the electrophile. This reaction is not shown in Scheme 49. In 2007 Rueping and Ieawsuwan[142] performed the reaction with quinoline derivatives and a number of other *N*-heterocycles. In 2008 Cahiez *et al.*[143] performed the reaction with various β-halostyrenes and other alkene halide derivatives. All these reactions are shown in Scheme 49.



Scheme 49: Manganese catalyzed Kumada cross-couplings by various groups.[136,139,140,142,143]

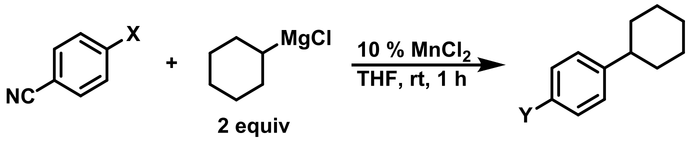
All these reactions used manganese(II) chloride or manganese(II) chloride bis(lithium chloride) in tetrahydrofuran at low temperature.

5.1. Previous Work by Collaborator

The work presented in this section have been performed by fellow Ph.D. student Giuseppe Antonacci. With focus on further developing and understanding the manganese cross-coupling, the reactions with aryl halide electrophiles were used as a basis for the study.

Based on the procedure of Cahiez *et al.*[140] initial studies were performed on the scope of the cross-coupling reaction. The reactions are shown in Table 23.

Table 23: Screening of 4-halobenzonitriles in the manganese catalyzed Kumada[144]

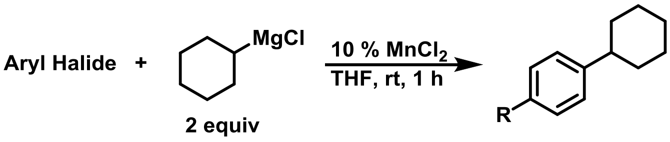


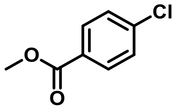
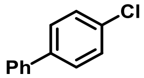
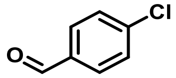
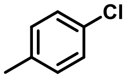
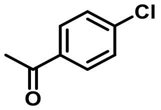
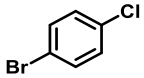
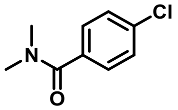
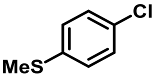
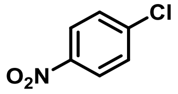
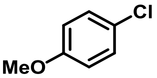
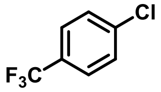
Entry	X	Y	Yield (%)[a]
1	Cl	CN	94
2	Br	CN	43
3	I	CN	-
4	F	CN	-

a) Isolated Yield

The reaction between 4-chlorobenzonitrile and cyclohexylmagnesium chloride was completed in 94 % yield (Entry 1), and the reaction with 4-bromobenzonitrile only gave 43 % yield (Entry 2). When a single equivalent of the Grignard reagent was used the reaction with 4-chlorobenzonitrile gave a low yield (reaction not shown). Using 4-iodobenzonitrile only resulted in the reduced starting material (Entry 3) and the reaction with 4-fluorobenzonitrile only gave the starting material (Entry 4). A number of electrophiles were screened for the reaction as shown in Table 24.

Table 24: Screening of the electrophile.



Entry	Aryl Halide	Yield (%)[a]	Entry	Aryl Halide	Yield (%)[a]
1		65	7		-
2		-	8		-
3		-	9		-
4		-	10		-
5		-	11		-
6		-			

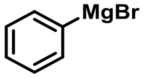
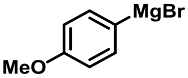
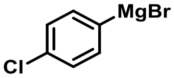
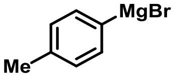
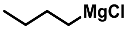
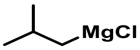
a) b) Isolated Yield

When methyl 4-chlorobenzoate was used as an electrophile, the reaction gave 65 % yield (Entry 1). When 4-chlorobenzaldehyde or -acetophenone was used, the nucleophile reacted at the carbonyl group (Entry 2 and 3) while *N*,*N*-dimethyl 4-bromobenzamide gave no reaction (Entry 4). Reaction with 4-chloronitrobenzene gave no trace of the product, but GCMS showed the formation of a reduced amine coupling product (Entry 5). Electrophiles with trifluoromethyl, phenyl, methyl, bromo, methylthio or methoxy substituents in the para position of phenyl chloride did not react with cyclohexylmagnesium chloride under these conditions (Entry 6-11).

Using iodo-, bromo- and chloro-nitrobenzene gave a trace of a compound with a mass equal to the reduced amine coupling product. Mixing manganese(II) chloride and phenylmagnesium bromide at – 78 °C before adding the electrophile and working up with iodine, resulted in homocoupling, phenyl iodide and the electrophile. Repeating this at -15 ^{0}C resulted in these products as well as a trace of the coupling product. A reaction with 1-chloro-4-(trifluoromethyl)benzene and phenylmagnesium chloride or bromide quenched with iodine at 50 ^{0}C gave phenyl iodide, homocoupling and the starting material.

The reaction was also screened for a number of different Grignard reagents. The screening with 4-chlorobenzonitrile is shown in Table 25 while the screening with 2-chlorobenzonitrile is shown in Table 26.

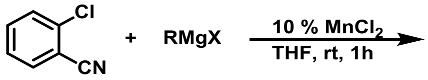
Table 25: Screening of nucleophiles in the reaction with 4-clorobenzonitrile.

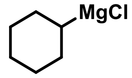
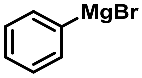
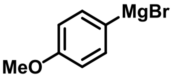
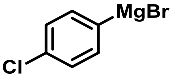
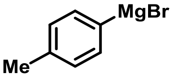
Entry	Nucleophile	Yield (%)^a
1		93
2		83
3		79
4		77
5		68
6		63^b
7		58

a) Isolated yield.
b) Yield based on NMR.

Phenylmagnesium bromide gave a good yield of 93 % (Entry 1) while 4-methoxyphenylmagnesium bromide, 4-chlorophenylmagnesium bromide and tolylmagnesium chloride gave slightly lower yields, 83 %, 79 % and 77 %, respectively (Entry 2-4). Reactions with alkylmagnesium chlorides gave moderate yields, 68 % for *n*-butylmagnesium chloride, 63 % for isobutylmagnesium chloride and 58 % using *tert*-butylmagnesium chloride (Entry 5-7).

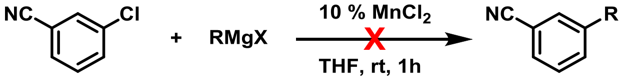
Table 26: Screening of nucleophiles in the coupling with 2-chlorobenzonitrile.



Entry	Nucleophile	Yield (%)[a]
1		91
2		90
3		80
4		79
5		78

a) Isolated Yield

When using 2-chlorobenzonitrile, the reaction with cyclohexylmagnesium chloride gave 91 % yield (Entry 1). This was comparable to the yield for the reaction with 4-chlorobenzonitrile (Table 23, Entry 1). Likewise, the reactions with phenylmagnesium bromide, 4-methoxyphenylmagnesium bromide, 4-chlorophenylmagnesium bromide, and 4-tolylmagnesium bromide gave 90 %, 80 %, 79 % and 78 % yield, respectively (Entry 2-5), all comparable to the reactions with 4-chlorobenzonitrile (Table 25, Entry 2-5). Reactions with 3-chlorobenzonitrile with various Grignard reagents gave no product. This experiment is shown in Scheme 50.



R: Cyclohexyl or Phenyl

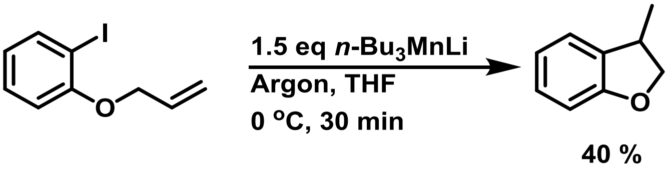
Scheme 50: Reaction with 3-chlorobenzonitrile

The reaction of 4-chlorobenzonitrile and phenylmagnesium chloride was tested at different temperatures. If the Grignard reagent was added at room temperature, the reactions would heat to reflux immediately due to the increase in temperature caused by the exothermic reaction. At 6 ^{0}C most of the starting material would be converted after a minute while only 5 % product would be formed after 2 hours at

0 °C. Quenching the reaction without the temperature rising above – 12 °C only gave the starting material.

The relative reactivity of the Grignard reagents was tested by reacting 4-chlorobenzonitrile with a mixture of phenylmagnesium chloride and cyclohexylmagnesium chloride. The major product of this reaction was 4-cyclohexylbenzonitrile while only trace amounts of 4-phenylbenzonitrile were observed. This indicates that the most nucleophilic Grignard reagent is also the most reactive. Likewise, a competition experiment between 4-chlorobenzonitrile and methyl 4-chlorobenzoate using cyclohexylmagnesium chloride was carried out. Here the reactivity was equally favored between the two electrophiles.

Testing methods for radical intermediates was considered. Using carbonyl compounds as trapping reagents were not considered because of the presence of the Grignard reagent. 1,4-Cyclohexadiene when added to a radical reaction with alkyl halides is reported to result in various products such as the homocoupling product, the dimerization product of cyclohexadiene, dehalogenated alkyl, coupling of the electrophile and cyclohexadiene[145] and benzene.[146] When added in the manganese catalyzed Kumada coupling, the only product was the cross-coupling product. Using the radical trapping reagent 2,2,6,6,-tetramethyl-1-piperidinyloxy (TEMPO) was reported in the literature to react with organometallic compounds to form the alkylated TEMPO and was therefore not attempted.[147] To trap a potential radical at the ipso halide position an intramolecular radical clock experiment was considered. Inoue *et al.*[148] had already shown 1-(allyloxy)-2-iodobenzene to be the precursor for 3-methyl-2,3-dihydrobenzofuran by using stoichiometric tributylmanganate as shown in Scheme 51.

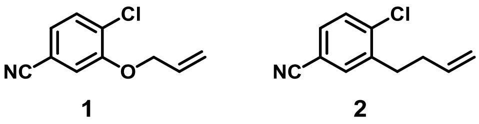


Scheme 51: Lithium tributylmanganate promoted cyclization.[149]

The magnesium species *n*-$Bu_3MnMgBr$ gave comparable yields when used instead of the lithium based complex. Interestingly, the use of *n*-BuMnCl or *n*-Bu_2Mn did not result in the formation of the cyclization compound and manganese(II) chloride had to be mixed with three equivalents of the Grignard reagents for the reaction to work. Inoue *et al.*[148] also discovered that the reaction could run with catalytic amounts of manganese(II) chloride by adding 4 equivalents of *n*-butylmagnesium chloride in THF at 25 ^{0}C. It was reported that this reaction did not run without the presence of oxygen.

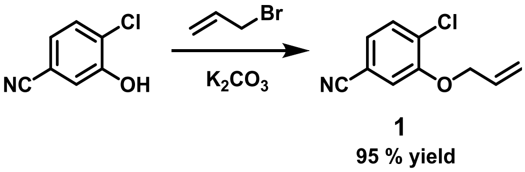
5.2. Results

To get an indication of whether the manganese catalyzed Kumada cross-coupling had a benzenyl radical intermediate, the synthesis of, and reaction with, 3-(allyloxy)-4-chlorobenzonitrile **1** and 3-(but-3-en-1-yl)-4-chlorobenzonitrile **2** was attempted. These compounds are shown in Scheme 52.



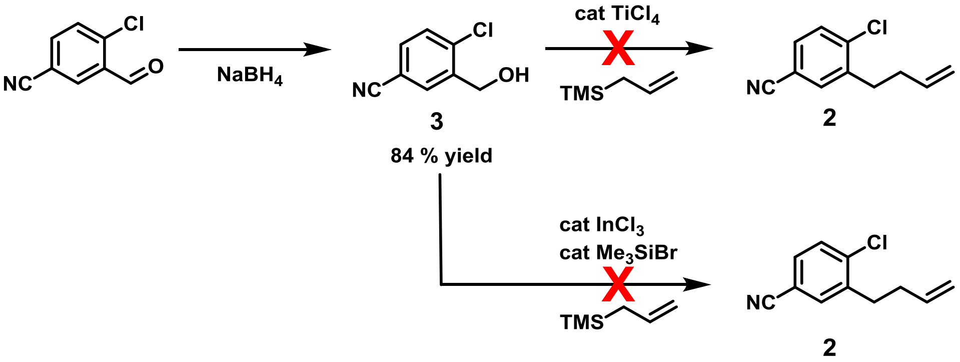
Scheme 52: 3-(allyloxy)-4-chlorobenzonitrile and 3-(but-3-en-1-yl)-4-chlorobenzonitrile.

4-Chloro-3-hydroxybenzonitrile was purchased and *O*-allylated under conditions inspired by the allylation of phenol by Choi *et al.*[150] The product **1** was isolated in 95 % yield as shown in Scheme 53.



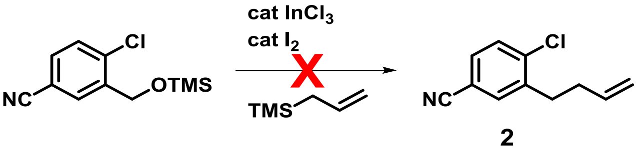
Scheme 53*: O-Allylation of 4-chloro-3-hydroxybenzonitrile.*

It was conceived that 3-(but-3-en-1-yl)-4-chlorobenzonitrile **2** could be formed from the corresponding benzyl alcohol, 4-chloro-3-(hydroxymethyl)benzonitrile **3**, which should be obtainable from the commercially available 4-chloro-3-formylbenzonitrile. The conditions chosen to reduce the aldehyde were taken from Ward and Rhee's[151] procedure for reducing benzaldehyde. This reaction, shown in Scheme 54, gave 84 % yield. *C*-Allylation of, among others, benzyl secondary alcohols with titanium(IV) chloride and allyl trimethylsilane was reported by Hassner and Bandi.[152] The reaction was reported to give good yields in under 15 minutes. When attempting this reaction with 4-chloro-3-(hydroxymethyl)benzonitrile **3**, the full starting material could be recovered after 30 minutes by extraction and concentration. Another method was therefore attempted. Saito *et al.*[153] reported the *C*-allylation of benzyl alcohol using a combined Lewis acid, indium(III) chloride and bromotrimethylsilane, to promote the reaction. This reaction resulted only in the trimethylsilyl ether benzyl product and the starting material. Subsequent attempts to achieve this reaction succeeded only in increasing the amount of the trimethylsilyl ether product. The reactions are shown in Scheme 54.



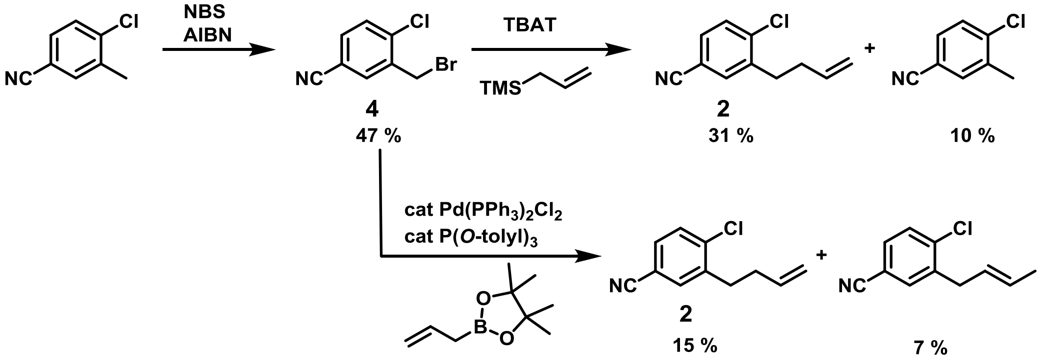
Scheme 54: Attempts at synthesizing of 3-(but-3-en-1-yl)-4-chlorobenzonitrile.

The same authors[153] also reported the allylation of trimethylsilyl ethers, using iodine instead of bromotrimethylsilane.[154] The reaction was attempted, shown in Scheme 55, but after 6 hours, GCMS showed no formation of the product.



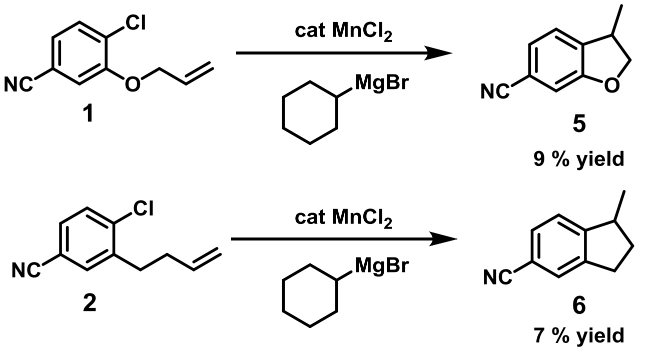
Scheme 55: Attempted allylation of the trimethylsilyl benzyl ether.

A new approach for the formation of 3-(but-3-en-1-yl)-4-chlorobenzonitrile was then adopted. Picher and DeShong[155] had reported a procedure for allylation of benzyl bromide using tetrabutylammonium difluorotriphenylsilicate (TBAT) and allyl trimethylsilane. To obtain the starting material for this reaction, a procedure for bromination using *n*-bromosuccinimide and azobisisobutyronitrile (AIBN), patented by Yoshida *et al.,*[156] was used giving the product in 47 % yield. The allylation was attempted which gave a 31 % yield, shown in Scheme 56. However, the product was inseparable from the reduced starting material, which was produced in around a 1:3 ratio to the desired product. Barely enough compound for a single reaction was produced, and since no more TBAT was available, another method was attempted. A Suzuki cross-coupling using conditions inspired by Shaber *et al.*[157] who had patented the coupling of 3-bromomethylbenzonitrile and phenylboronic acid, was carried out. The reaction, shown in Scheme 56, resulted in 15 % product and 7 % of alkene migration by-product. The GCMS indicated a mass corresponding to the Heck product but this was not isolated. The product and the migrated product could not be separated by flash chromatography.



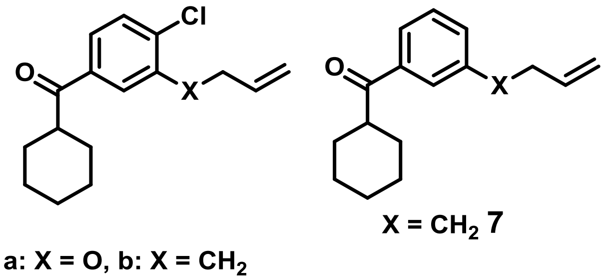
Scheme 56: Synthesis of 3-(but-3-en-1-yl)-4-chlorobenzonitrile.

The byproduct resulting from migration was not expected to cause complications in a radical cyclization experiment. The reaction had been performed on a larger scale and there was therefore enough product available to attempt a clock reaction. The manganese catalyzed Kumada cross-coupling was attempted with 3-(allyloxy)-4-chlorobenzonitrile **5** and 3-(but-3-en-1-yl)-4-chlorobenzonitrile **6** resulting in 9 % and 7 % cyclization product, respectively. The reactions are shown in Scheme 57.



Scheme 57: Clock experiments.

The result of the reactions was a mixture of compounds and most of them were never isolated and identified. The mass of the ketone formed through addition to the nitrile was detected for both reactions, but only in the second reaction was this product, (3-(but-3-en-1-yl)-4-chlorophenyl)(cyclohexyl)methanone **7**, isolated in 12 % yield. This compound, and other sideproduct suspected of being present is shown in Scheme 58.



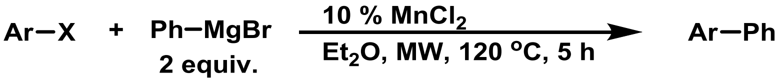
Scheme 58: Some possible byproducts of the clock experiment.

Only small peaks with a mass corresponding to the coupling products with the Grignard reagents were present in the GCMS spectra. The coupling product for the ether was not isolated. The compound with a mass corresponding to 3-(but-3-en-1-yl)-4-cyclohexylbenzonitrile was traced to a fraction that could contain no more than 3 % yield, but was not purified enough to obtain a clean spectra.

5.3. Further Developments

The work presented in this section was performed by fellow Ph.D. students Carola Santilli and Somayyeh Sarvi Beigbaghlou. By performing the cross-coupling reaction in a microwave oven at 120 °C, it was possible to extend the scope beyond cyano- and ester-activated aryls.[158] The conditions and scope are shown in Table 27.

Table 27: Manganese catalyzed arylation of aryl halides.[158]



$$\mathrm{Ar{-}X} + \underset{\text{2 equiv.}}{\mathrm{Ph{-}MgBr}} \xrightarrow[\mathrm{Et_2O,\ MW,\ 120\ ^\circ C,\ 5\ h}]{10\ \%\ \mathrm{MnCl_2}} \mathrm{Ar{-}Ph}$$

Entry	Substrate	Yield %
1	4-iodotoluene	66[b]
2	4-bromotoluene	47[b]
3	3-iodotoluene	55[b]
4	2-iodotoluene	34[b]
5	4-iodo-1,2-dimethylbenzene	77
6	1-iodo-3,5-dimethylbenzene	62[b]
7	3-iodoanisole	26
8	4-iodoanisole	23
9	3-iodo-*N,N*-dimethylaniline	33
10	4-iodo-*N,N*-dimethylaniline	28

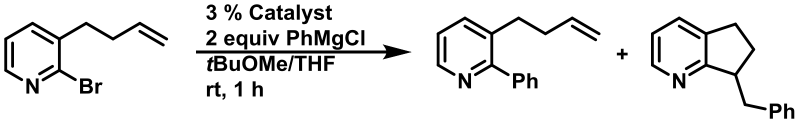
a) Isolated yield
b) Yield based on NMR since the isolated product was not completely pure.

The reaction in Entry 1 was repeated with 10 equivalents of cyclohexa-1,4-diene which gave 7 % of the cross-coupling product and 56 % of the dehalogenated starting material. Also 4-(2-bromophenyl)-but-1-ene was subjected to the reaction with phenylmagnesium bromide and resulted in 41 % of the cyclization products and 5 % product.[158]

5.4. Discussion

The substrates used by Rueping and Ieawsuwan[142] and Cahiez *et al.*[140] are all electron poor substrates or contain electron withdrawing groups. Reactions between the Grignard reagent and 4-bromoquinoline or 1-(4-iodophenyl)-*N*-isopropylmethanimine affords the halogen/manganese exchange products.[159,160] Aryl Grignard reagent could participate in a heterocoupling to provide the products. However, such a reaction would require careful addition of oxygen[161] likely to facilitate the reductive elimination.[162,163] Rueping and Ieawsuwan[142] use 1.5

equivalents Grignard reagents and achieve yields well above 75 % while Cahiez *et al.*[140] uses two equivalents. Grignard reagents can add to activated pyridines, such as pyridine 1-oxide, resulting in ring opening.[164] Halogen substituted heteroaromats are known to react as electrophiles in nucleophilic aromatic substitution. For example, 2-chloropyridine reacts with alkoxides at 65 °C. However, direct use of Grignard reagents with iodo- and bromopyridines result in halogen-metal exchange[165] while a literature search revealed no examples of substitution with a Grignard nucleophile to chloropyridine when no transition metal was present. The metal catalyzed cross-coupling of choro-*N*-heterocycles is known with palladium, nickel, iron, cobalt and chromium catalysts.[166–169] Palladium and nickel were the only catalysts that had examples of couplings with chlorides in the 3-position to the nitrogen, in comparable yields to the 2-position counterparts. These reactions show that the conjugation is not needed for the reaction and count as evidence that the reaction is a cross-coupling. Kuzmina *et al.*[169] have included a clock experiment for iron, cobalt, nickel and palladium as shown in Scheme 59.



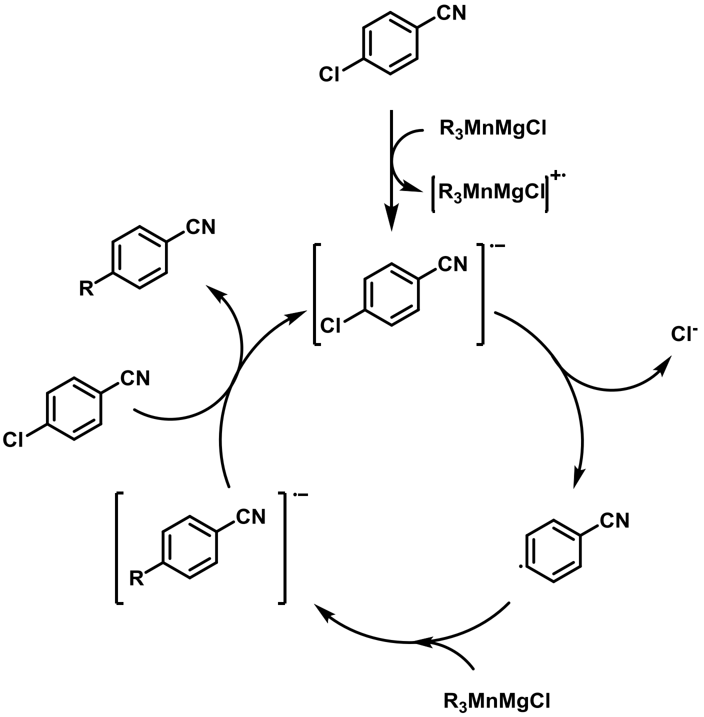
Scheme 59: Cyclization clock experiment by Kuzmina *et al.*[169]

The palladium clock experiment reaction was performed with tetrakis(triphenylphosphine)palladium(0) as catalyst was performed at 50 °C and gave only the cross-coupling product. 1,2-Ethylenebis(diphenylphosphine)-nickel dichloride as catalyst gave 5 % cyclization product while iron(III) bromide and cobalt dichloride both gave 20 % of the cyclization product, which is an indication of radical intermediates. Also 10 % of isoquinoline increased the yield for both the iron and the cobalt reaction, while not changing the cross-coupling/cyclization product ratio.[169] Steib *et al.*[168] performed a cobalt catalyzed reaction with the same substrate, but achieved solely of the cross-coupling product in 95 % yield and observed no cyclization product. The cobalt and iron catalyzed clock experiments could be indicating a $S_{RN}1$ reaction. Such a mechanism had previously been suggested for 2-chloropyridines using sodium thiophenol at 80 °C.[170] These results indicate that at least two mechanisms are at play for the different metals although it gives no indication of what the mechanism is for the manganese catalyzed cross-coupling.

The radical cyclization clock experiment, shown in Scheme 59, is comparable to the reactions shown in Scheme 57 and indicate the formation of an aryl radical intermediate. The cyano group is known to stabilize the radical anion in chloro cyanobenzene.[171] The rate of dehalogenation of the 4- and the 2-chlorobenzonitrile radical anion is on the order $5{\cdot}10^{-6}$ s^{-1} and $9{\cdot}10^{-6}$ s^{-1} while the dehalogenation rate of 3-chlorobenzonitrile radical anion is several orders of magnitude lower at $4{\cdot}10^{-4}$ s^{-1}. These rates are at least an order of 5 magnitudes higher than for the corresponding halo nitrobenzene.[172] The reason that 3-chlorobenzonitrile does not react (Scheme 50) could be due to the decrease in stability of the radical anion. The failed reaction with 4-fluorobenzonitrile (Table 23, Entry 4) indicates that the reaction is not an aromatic nucleophilic substitution (S_NAr) as the fluoride is usually a better leaving group for this mechanism.[173] This is in contrast to the reaction with tolylideneamine derivatives from Cahiez *et al.,*[140] who achieved comparable yields with fluoro-, chloro-, bromo-, and methoxy- leaving groups. The methoxy group needs reaction temperatures at 20 ^{o}C, compared to 0 ^{o}C for the halides,[140] in accordance with it being a poorer leaving group.[173] The reason why the nitrobenzene cross-coupling product is not observed (Table 24, Entry 5) is likely due to the reductive *N*-arylation of nitroarenes,[174] which would explain the observation of a peak with a mass corresponding to that of the diarylamine. The atom economy of this reaction can be improved by reducing the hydroxylamine in a separate step as reported by Sapountzis and Knochel.[175] 1-Chloro-4-(trifluoromethyl)benzene does not react, despite trifluoromethyl group having a Hammett constant close to that of the cyano group, 0.54 for trifluoromethyl and 0.66 for the cyano group respectively.[176] With a cross-coupling mechanism these compounds are expected to undergo oxidative addition at about the same rate resulting in the same overall reactivity.

The reaction reported by Rueping and Ieawsuwan[142] does not contain sufficient information to allow for a speculation about the mechanism. The reactions reported by Bouissed and Boudin[136] with 2-chlorobenzonitrile, and that of Cahiez *et al*,[140] with tolylidenenamines, likely follows two different mechanisms.

Inoue *et al.*[148] showed the reaction with 1-(allyloxy)-2-iodobenzene to be the precursor for 3-methyl-2,3-dihydrobenzofuran by using stoichiometric tributylmanganate as shown in Scheme 51. The reaction could also be performed with *n*-$Bu_3MnMgBr$ which gives comparable yields or be performed with catalytic amounts of manganese(II) chloride and using 4 equivalents of the Grignard reagent. Using one or two equivalents to form a manganese reagent resulted in no reaction.[148] The catalytic reaction was performed at 25 °C and the cyclization yield increased when oxygen was injected.[148] Based on their suggested mechanism, a trialkylmanganate complex reduces the starting material followed by dehalogenation and cyclization, and a similar reaction mechanism can be drawn for the reaction with 4-chlorobenzonitrile. The reaction is shown in Scheme 60.



Scheme 60: Possible reaction mechanism for the manganese catalyzed Kumada radical reaction.

The cyclization reaction at 120 ^{o}C in the microwave oven shows that a radical can be formed with 4-(2-bromophenyl)-but-1-ene and indicates that the reaction for the expanded scope could be the same reaction. With the cyano group removed, the reaction could be performed with aryl iodides.

5.5. Conclusion

The manganese catalyzed Kumada cross-coupling of aryl halides has a limited scope and despite similar conditions the scope indicates that more than one mechanism might be at play. The scope and mechanistic studies indicate neither a catalytic cross-coupling mechanism nor a nucleophilic aromatic substitution when a cyano group is present. Instead the general scope and a clock experiment points towards a radical mechanism.

5.6. Experimental Data

General Information:

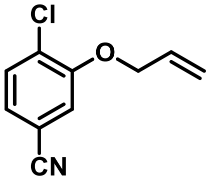
All solvents where of HPLC grade and were used without further purification. Flash column chromatography separations were performed on silica gel 60 (40 – 63 μm). NMR spectra where recorded on a Bruker Ascend 400 spectrometer. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.16 ppm).[177] HRMS measurements where made using ESI with TOF detection. All Grignard reagents were obtained from commercial suppliers and titrated with a 0.06 M solution of I_2 in Et_2O to determine the concentrations: Cyclohexylmagnesium chloride (1.8 M in Et_2O).

General Procedure for Cross-Coupling

A dry three-neck Schlenk tube was equipped with a stir bar and a nitrogen inlet. $MnCl_2$ (25 mg, 0.2 mmol) was added and the flask was flushed with nitrogen and dry THF (6 mL) was added. The mixture was stirred for about 10 minutes to completely dissolve $MnCl_2$ followed by addition of the aryl halide (2 mmol) and cooling to 0 °C in an ice bath. A solution of the Grignard reagent (4 mmol) was added dropwise over 5 minutes and the ice bath was removed. The mixture was stirred for 1 h at ambient temperature. The reaction was quenched with a saturated ammonium chloride solution (10 mL). The mixture was extracted with EtOAc (4 ×

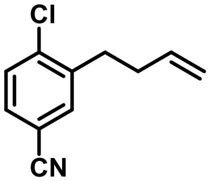
10 mL) and the combined organic layers were concentrated and the residue purified by flash column chromatography.

3-(Allyloxy)-4-chlorobenzonitrile (1):



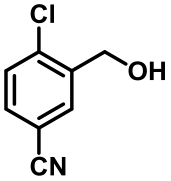
A mixture of 4-chloro-3-hydroxybenzonitrile (1 g, 6.5 mmol), allyl bromide (0.6 mL, 7.1 mmol) and K_2CO_3 (1 g, 7.2 mmol) in acetone (50 mL) was stirred under reflux. The reaction was monitored by TLC and additional allyl bromide (0.6 mL, 7.1 mmol) and K_2CO_3 (1 g, 7.2 mmol) were added after 20 min. After two hours, the reaction was diluted with water and extracted with diethyl ether. The organic layers were concentrated to give 1.2 g (95%) of a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.14 (s, 1H), 6.04 (ddd, J = 15.8, 10.5, 5.2 Hz, 1H), 5.48 (d, J = 15.8 Hz, 1H), 5.37 (d, J = 10.5 Hz, 1H), 4.64 (d, J = 5.0 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 131.6, 131.3, 129.0, 125.3, 118.9, 118.2, 116.4, 111.5, 70.1 ppm. HRMS: calcd for $C_{10}H_8ClNNaO$ 216.0186 [M + Na]$^+$, found: 216.0188.

3-(But-3-en-1-yl)-4-chlorobenzonitrile (2):



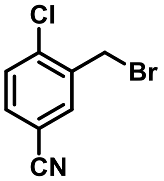
The procedure was inspired by a literature protocol for Suzuki couplings with benzyl bromides.[157] A mixture of 3-(bromomethyl)-4-chlorobenzonitrile (2.4 g, 10 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.75 g, 1 mmol), tri(*o*-tolyl)phosphine (325 mg, 10 mmol), allylboronic acid pinacol ester (1.97 g, 12 mmol) and Na_2CO_3 (2.15 g, 20 mmol) in aqueous acetonitrile (1/10 H_2O/MeCN, 100 mL) was stirred at reflux for 2 h. Water was added and the mixture was extracted with Et_2O. The organic layers were concentrated and the residue purified by column chromatography (4/1 pentane/CH_2Cl_2) to give 439.5 mg (22%) of the product as a brown oil, which contained about 30% of a byproduct where the olefin had migrated. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 1.7 Hz, 1H), 7.40–7.38 (m, 2H), 5.78 (ddt, J = 16.9, 10.3, 6.5 Hz, 1H), 5.02–4.98 (m, 1H), 4.98–4.95 (m, 1H), 2.80 (dd, J = 8.7, 6.7 Hz, 2H), 2.37–2.29 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 139.3, 136.7, 133.9, 130.8, 130.5, 118.2, 116.1, 110.8, 33.1, 32.8 ppm. HRMS: calcd for $C_{11}H_{10}ClNNa$ 214.0394 [M+Na]$^+$, found: 214.0401.

4-Chloro-3-(hydroxymethyl)benzonitrile (3)



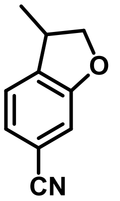
Inspired by a procedure from Prevost *et al.*[178] sodium borohydride (1.15 g, 30 mmol) was added to 4-chloro-3-formylbenzonitrile (5 g, 30 mmol) in absolute ethanol (50 mL) at -78 ^{o}C. The solution was allowed to heat to rt while stirred for 1.5 h. The reaction was quenched with saturated NH_4Cl and extracted with ether. Recrystallization with EtOAc/heptane gave 4.275 g (85 %) of the product as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.87 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 8.2, 2.9, Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 4.82 (s, 2H), 2.07 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 140.3, 137.3, 132.0, 131.6, 130.3, 118.3, 111.2, 61.8.

3-(Bromomethyl)-4-chlorobenzonitrile (4):



Inspired by the procedure by Imai *et al.*[156] : To a stirred solution of 4-chloro-3-methylbenzonitrile (5 g, 33 mmol) in 3,3-dimethylbutyric acid (50 mL), *N*-bromosuccinimide (7.5 g, 42 mmol) and azobisisobutyronitrile (0.25 g, 1.3 mmol) were added and the solution was heated at 90 ^{o}C for 12 hours. The reaction was quenched with saturated sodium hydrogen carbonate and extracted with ethyl acetate. Recrystallization (ethyl acetate/heptane) followed by column chromatography (5 % ethyl acetate/heptane) gave 3.6 g (47 %) of the product as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.75 (d, *J* = 1.8 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.52 (s, 1H), 4.55 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.5, 137.3, 134.7, 133.1, 131.2, 117.5, 111.7, 28.6. HRMS: calcd. For $C_8H_6BrClN^+$ [M+H$^+$]: 229.9367; found: 229.9365.

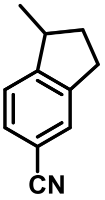
3-Methyl-2,3-dihydrobenzofuran-6-carbonitrile (5):



Allyl ether **1** (386 mg, 2 mmol) was reacted with cyclohexylmagnesium chloride and $MnCl_2$ as described above in the general procedure and purified with flash column chromatography (1/4 CH_2Cl_2/pentane) which gave 30.1 mg (9%) of the product as a brown oily solid. ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 7.21 (d, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.99 (d, *J* = 1.2 Hz, 1H), 4.74 (t, *J* = 9.0 Hz, 1H), 4.14 (dd, *J* = 8.8, 7.4 Hz, 1H), 3.65–3.50

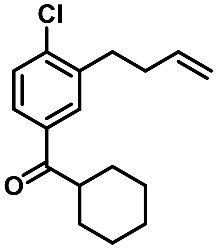
(m, 1H), 1.34 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 160.0, 138.5, 125.3, 124.7, 119.2, 112.7, 111.6, 79.1, 36.6, 19.1 ppm. HRMS: calcd for $C_{10}H_9NNaO$ 182.0576 [M + Na]$^+$, found: 182.0577.

1-Methyl-2,3-dihydro-1H-indene-5-carbonitrile (6):



Butenyl compound **2** (382 mg, 2 mmol, including 30% of the olefin isomer) was reacted with cyclohexylmagnesium chloride and $MnCl_2$ as described above in the general procedure and purified with flash column chromatography (1/4 CH_2Cl_2/pentane) which gave 21.7 mg (7%) of the product as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (s, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 3.27–3.17 (m, 1H), 2.94 (ddd, *J* = 16.2, 8.7, 4.0 Hz, 1H), 2.86 (dt, *J* = 16.4, 8.5 Hz, 1H), 2.35 (dtt, *J* = 11.4, 7.4, 3.7 Hz, 1H), 1.65 (dq, *J* = 12.6, 8.7 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 154.6, 145.2, 130.7, 128.1, 124.1, 119.8, 109.9, 39.9, 34.5, 31.3, 19.5 ppm. HRMS: calcd for $C_{11}H_{12}N$ 158.0964 [M + H]$^+$, found: 158.0964.

(3-(But-3-en-1-yl)-4-chlorophenyl)(cyclohexyl)methanone (7):

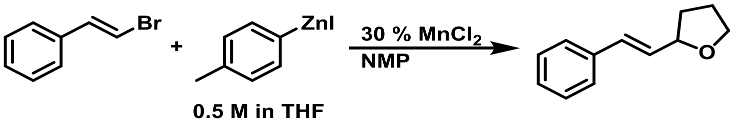


Purification of the reaction that gave **6** also gave **7** in 67.3 mg (12 % yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 2.3 Hz, 1H), 7.70 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 5.87 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.06 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.01 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.19 (tt, *J* = 11.3, 3.2 Hz, 1H), 2.87 (dd, *J* = 8.9, 6.8 Hz, 2H), 2.44-2.34 (m, 2H), 1.85 (tt, *J* = 9.5, 4.4 Hz, 4H), 1.78-1.69 (m, 1H), 1.54-1.23 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 203.0, 139.9, 138.9, 137.4, 134.9, 130.3, 129.8, 127.3, 115.7, 45.7, 33.6, 33.1, 29.5, 26.0, 25.9. HRMS: calcd. For $C_{17}H_{22}ClO^+$ [M+H$^+$]: 277.1354; Found: 277.1346.

6. Dimethyl Zinc Mediated Radical Alkylation of β-Bromostyrenes

6.1. Background for the Study

Sølvhøj[125] has previously studied the manganese catalyzed cross-coupling reactions and her initial attempts to validate the manganese catalyzed Stille cross-couplings failed. A manganese catalyzed reaction similar to that reported by Cahiez *et al.*[143] between β-bromostyrene and arylmagnesium chloride catalyzed by manganese(II) chloride was also attempted. Manganese(II) chloride tetrahydrate was used for this validation, which might be why no product was obtained at room temperature, as reported in the literature. At 50 °C the reaction resulted in full conversion with transstilbene as the major product. When no catalyst was used, the reaction was 'nowhere near completion' and the extend of homocoupling was 'considerably pronounced'. A reaction with organozinc was hypothesized based on the principle that it was a similar reagent with regards to nucleophilicity, basicity and reductive abilities. Unexpectedly, the reaction led to a coupling with the solvent THF. The conditions for the initial reaction are shown in Scheme 61.[125]



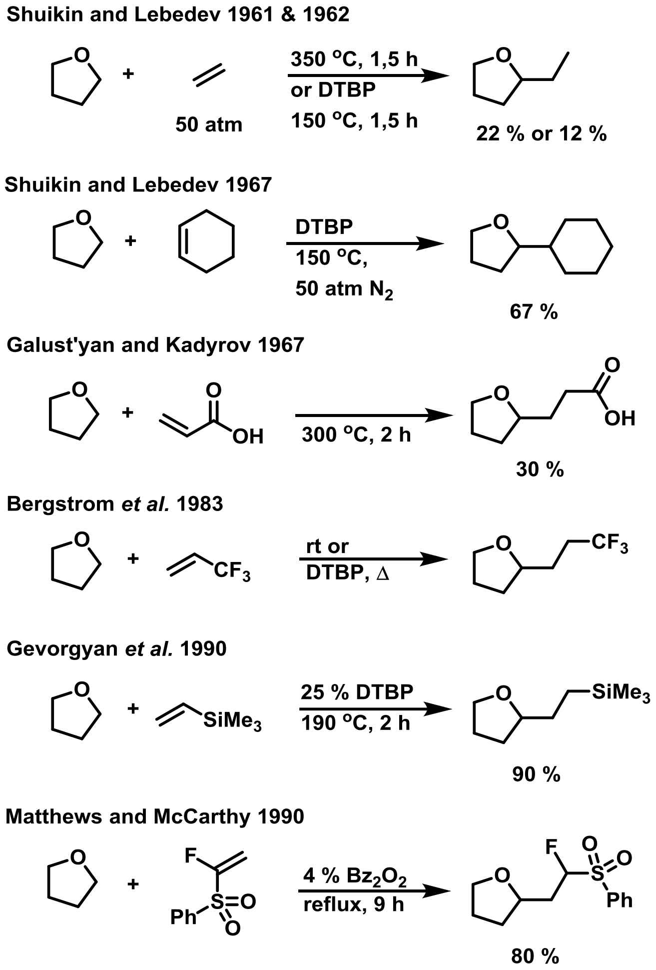
Scheme 61: Radical β-alkylation of β-bromostyrne by Sølvhøj.[125]

Similar reactions of β-bromostyrenes with organozinc halides run in THF at room temperature can be catalyzed by palladium complexes to give high yields of the cross-coupling product.[179]

This reaction started as a study of the manganese catalyzed Negishi cross-coupling, but ended after optimization as a dimethylzinc-initiated radical coupling reaction.[180] For this reason, the following introduction and background section will be about radical coupling of styrenes, while the overall text will contain comparisons to transition metal catalysis.

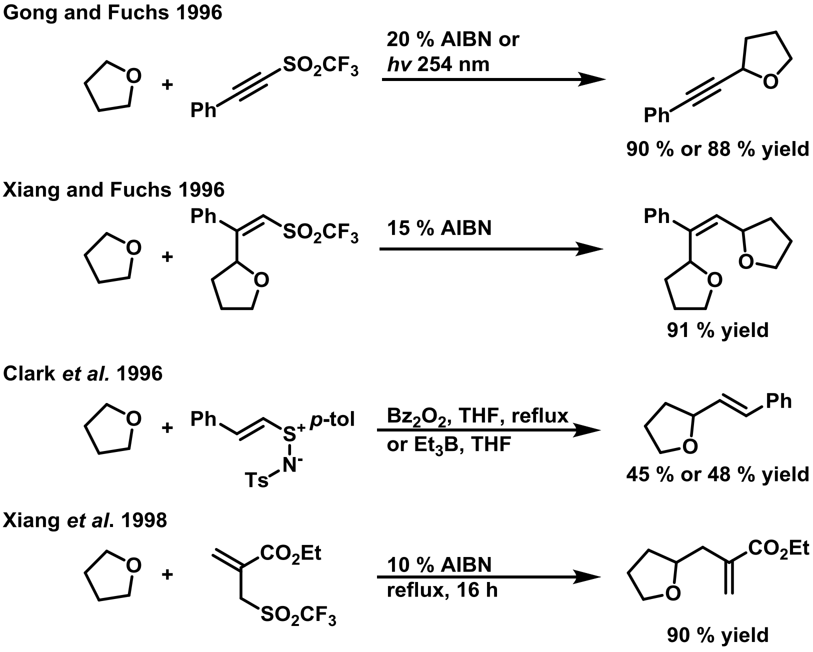
6.2. α-Tetrahydrofuranyl Radicals from Tetrahydrofurans

α-Tetrahydrofuranyl radicals have been used in synthetic chemistry since it was discovered by Shuikin and Lebedev that they could be alkylated with ethene at temperatures around 300-400 ^oC. Subsequently, the use of di-*tert*-butyl peroxide (DTBP) allowed the temperature to be lowered by about 100 ^oC.[181] The scope was expanded to include unsaturated ethers[182] and unsaturated acids in addition to longer alkenes by Galust'yan and Kadyrov.[183] Bergstrom *et al.*[184] reported on the degradation reaction with 3,3,3-trifluoropropene where a side reaction of 1,5-hydride shift was noted. Gevorgyan *et al.*[185] reported on the reaction with vinyl- and allyl silanes. Matthews and McCarthy[186] used benzoyl peroxide or zinc dust as initiators for the reaction with 1,1-phenylsulfonyl-fluoro-ethylene and tetrahydrofuran. These reactions are shown in Scheme 62.



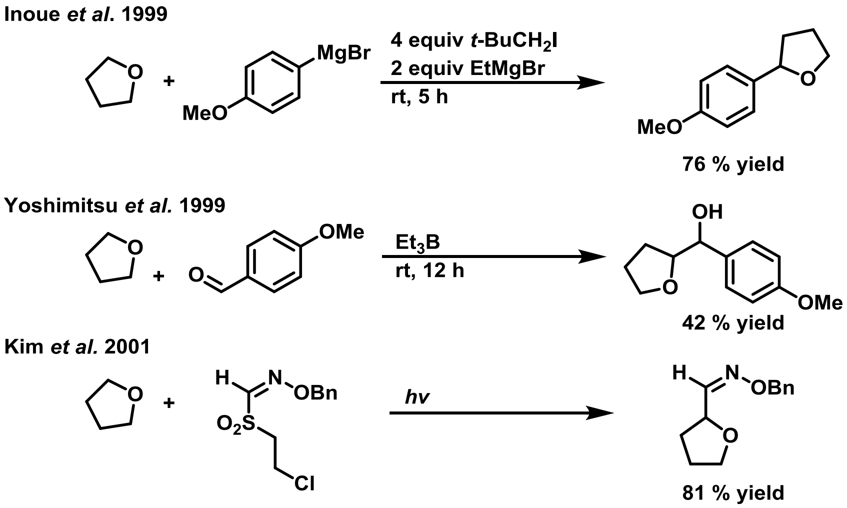
Scheme 62: Early use of α-tetrahydrofuranyl radical in synthesis.

In 1996 Gong and Fuchs[187] used azobisisobutyronitrile (AIBN) and light (254 nm) for alkylation of acetylenic triflones. Using no initiator gave a good yield which was attributed to trace peroxides and an autocatalytic effect. However using other substrates such as *tert*-butyl methyl ether gave no product without added radical initiator. Xiang and Fuchs[188] used trifluoromethylsulfones for the alkylation of alkenes while Xiang *et al.*[189] alkylated trifluoromethylsulfonyl allyls. After addition of the α-tetrahydrofuranyl radical, the newly formed radical degrades thereby releasing the trifluoromethylsulfonyl group. This species fragments into sulfur dioxide and a trifluoromethyl radical that exctracts a hydrogen under formation of a new α-tetrahydrofuranyl radical. Trifluoromethylsulfonyl substrates are therefore able to regenerate their π-bonds, resulting in an overall substitution reaction. Clark *et al.*[190] alkylated unsaturated sulfimides but had to use stoichiometric amounts of an initiator.



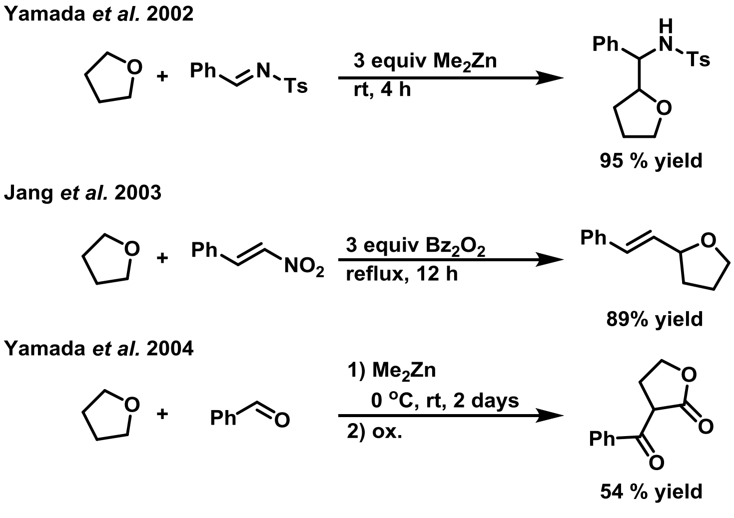
Scheme 63: Alkylation of unsaturated sulfur species.[188–191]

In 1999 Inoue *et al.*[192] reported the α-arylation of THF. They suggested the single electron transfer (SET) from ethylmagnesium bromide to the alkyl iodide and the subsequent degradation, leading to an alkenyl radical that could abstract the α-hydrogen of THF. The α-tetrahydrofuranyl radical would abstract an iodide from an alkyl iodide resulting in an overall *in situ* α-halogenation, followed by reaction with the aryl Grignard reagent. The same year Yoshimitsu *et al.*[193] used triethylborane in the alkylation of aldehydes. The Lewis acid effect of the borane led to a diastereoselective addition. Kim *et al.*[194] used a 2-chloroethylsulfonyl oxime ether in the formation of tetrahydrofuran imines. The addition reaction released sulfur dioxide and ethene while a chlorine radical formation ensured the formation of a new tetrahydrofuranyl radical.



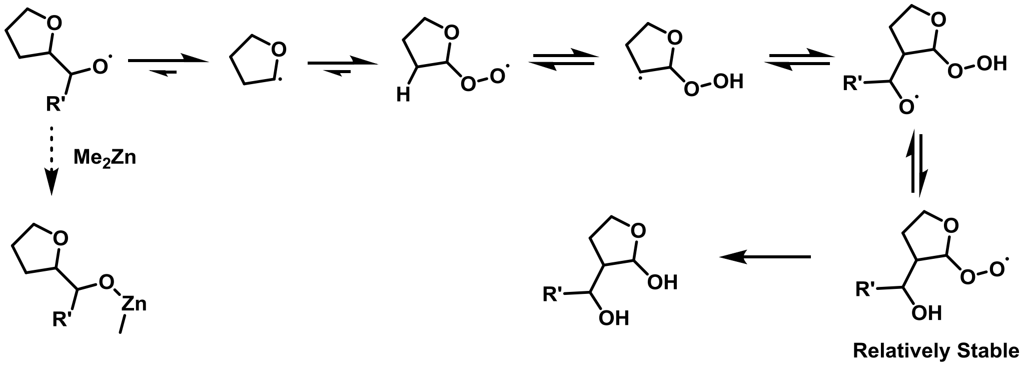
Scheme 64: Examples of α-tetrahydrofuranyl radicals in reactions.[192–194]

In 2002 Yamada *et al.,*[195] who had been researching alkylation of imines with dialkylzinc, discovered that when they used dimethylzinc the product was the addition product from a α-tetrahydrofuranyl radical addition, instead of the expected methylated product. Jang *et al.*[196] added α-tetrahydrofuranyl to styrene by an addition-elimination reaction releasing the nitro group. In 2004 Yamada *et al.*[197] used dimethylzinc as an initiator in the reaction with THF and aldehydes, giving an unexpected product shown in Scheme 65.



Scheme 65: Dimethylzinc as intiator and the nitro group for addition-elimination reactions.[195–197]

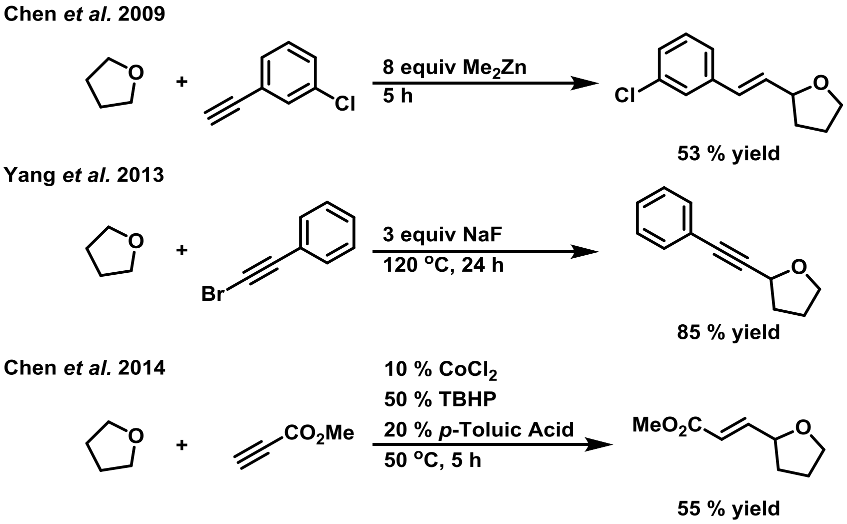
For the addition reactions to imines and aldehydes there is orthogonality between triethylborane and dimethylzinc. Addition of triethylborane to a mixture of an aldehyde and a primary amine will give primarily the addition to the aldehyde, while using dimethylzinc as initiator will give the imine addition product.[198] The reactivity of the dimethylzinc-initiated addition to aldehydes is explained by the slow stabilization of the addition product as shown in Scheme 66.



Scheme 66: Possible mechanism for β-addition with dimethylzinc initiated aldehyde addition.[197]

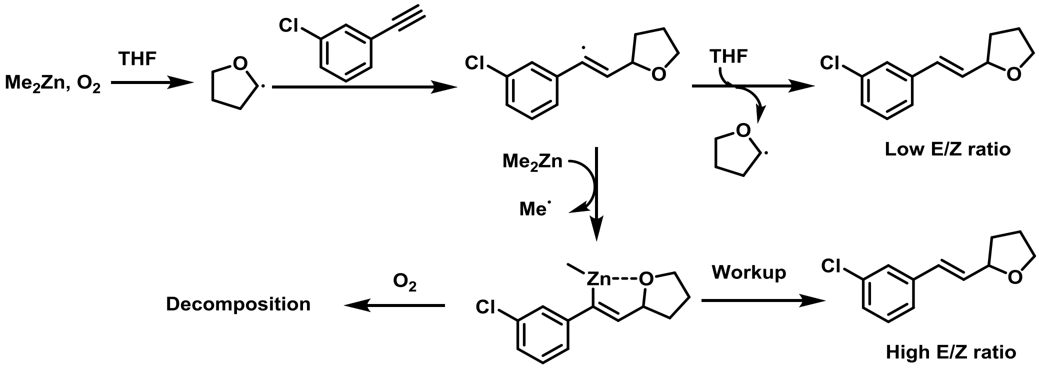
The stabilization of the ketyl radical from the addition to an aldehyde by the borane initiator facilitates the reaction as well as guide the stereochemistry.[193] Using benzoyl peroxide with imines gives the starting material, probably due to the lack of stabilization of the radical addition species.[195] The reaction of the aldehyde with a peroxide initiator was not found in the literature. The higher temperature required for activation of benzoyl peroxide, and therefore loss of selectivity could result in a side reaction from the extraction of the aldehyde proton.

In 2009 Chen *et al.*[199] used dimethylzinc as initiator for the addition of tetrahydrofuran to an arylacetylene forming the styrene with high E/Z ratio. Optimization of the oxygen/nitrogen atmosphere of the reaction was performed and showed that a 1:1000 ratio was optimal. When triethylborane was used as an initiator, the selectivity was reversed. Yang *et al.*[200] used sodium fluoride at high temperatures for a radical substitution of aryl bromoacetylenes, showing that a halide could function as a leaving group similar to the substitution on styrenes, that Jang *et al.*[196] had shown for nitro groups ten years earlier. Chen *et al.*[201] showed that a transition metal, cobalt(II) chloride, facilitated a radical addition to acetylene substrates. The mechanism of the reaction is unknown but it requires *tert*-butyl hydroperoxide, acid and the transition metal to work and shuts down in the presence of TEMPO.



Scheme 67: Radical addition to acetylene acceptors.[199–201]

The selectivity of the dimethylzinc initiated radical addition to arylacetylenes is attributed to the stabilization of the alkenyl radical intermediate by methylzinc, as shown in Scheme 68.[199]



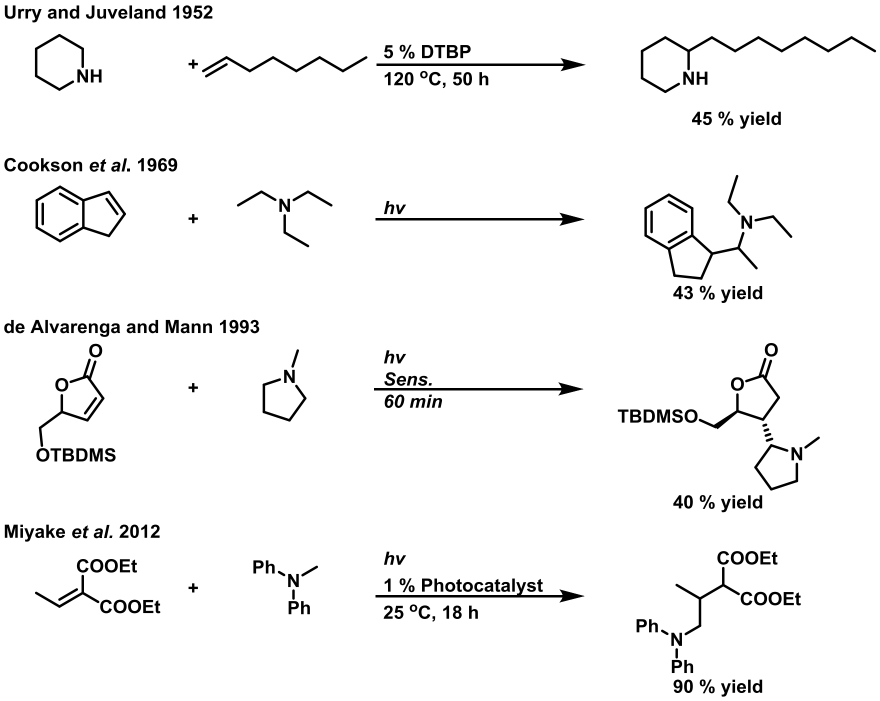
Scheme 68: Suggested mechanism for radical addition to arylacetylene.[199]

In all of the above reactions generating an alkene, the stereochemistry depends on the radical initiator as well as the starting material. When Clark *et al.*[190] used benzoyl peroxide with the *E*-isomer, it retained the stereochemistry while using the

Z-isomer resulted in a mixture of products. When triethylborane was used as a radical initiator, the stereochemistry was retained with both isomers. Xiang and Fuchs[188] use of azobisisobutyronitrile (AIBN) in the reaction with trifluoromethylsulfonyl styrene resulted in the *E*-isomer regardless of the stereochemistry of the starting material. Jang *et al.*[202] observed the same stereoselectivity when benzoyl peroxide was used with nitrostyrenes.

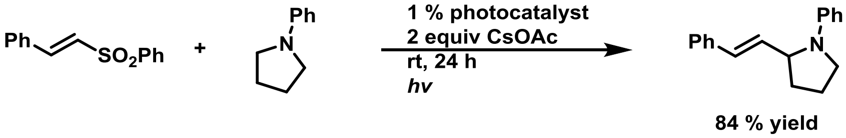
6.3. α-Aminoalkyl Radicals

The α-aminoalkyl radical have been less exploited in synthetic chemistry. As early as 1952 it was shown by Urry and Juveland[203] that an α-aminoalkyl radical could be generated with peroxides at high temperature and added to an alkene to form the alkylamine. Cookson *et al.*[204] found that irriadiation of styrenes and trimethylamine leads to the addition of the radical at the C-1 position while trimethylamine added to the β-position of unsaturated ketones and esters.[205] In 1993 de Alvarenga and Mann[206] used benzophenone as sensitizer to promote the reaction of *N*-methylpyrrolidine and a 5-alkylfuran-2(5H)-one. Later a transition metal photocatalyst, such as iridium polypyridyl as reported by Miyake *et al.,*[207] was used. The reactions are shown in Scheme 69.



Scheme 69: Reactions with α-aminoalkyl radicals.[204,206–208]

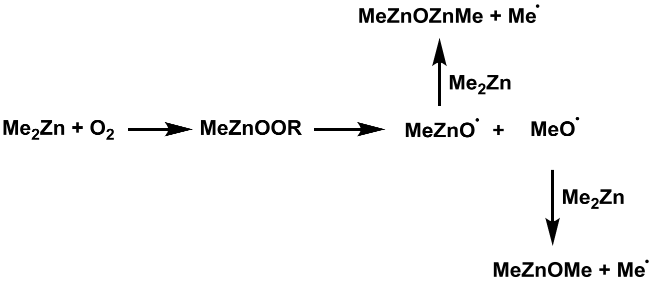
Chemical oxidation forming an α-aminoalkyl radical was generally hindered by their tendency to further oxidize to the iminium ion.[209] Using benzoyl peroxide at lower temperatures as presented with ethers above was not found described in the literature, likely because of the fact that quick reactions with amines caused explosions.[208] Using sensitizers do not result in further oxidation to the iminium ion[209] but the first sensitizer, benzophenone, did not result in high yields.[206] Bertrand *et al.*[210] suspected side reactions with the α-aminoalkyl radical and the exited sensitizer to be part of the reason for the low reactivity. The result of their study was a modified sensitizer that had electron rich substituents to limit its reactivity with the nucleophilic radical amine. The results for these reactions were lower loading of the sensitizer, higher yields and making the sensitizer recoverable. Noble and MacMillan[211] expanded the scope by using vinyl sulfones as radical acceptors and exploited them as leaving groups, similar to that shown with α-tetrahydrofuranyl radicals above. This reaction is shown in Scheme 70.



Scheme 70: α-Alkylation of *N*-phenylpyrrolidine with photocatalyst by Noble and MacMillan.[211]

6.4. Dimethylzinc in Synthesis

Dimethylzinc is pyrophoric. When it is used with secondary amines under inert conditions, methylzinc amines are generated.[212] Adding carbon dioxide to the solution leads to a carbonylated amine zinc complex.[213] The activation of dimethylzinc is proposed to go through the steps shown in Scheme 71.



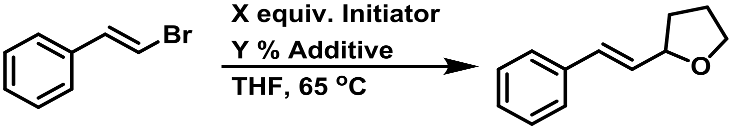
Scheme 71: Proposed initiation of dimethylzinc.[214]

The mechanism suggests that three equivalents of dimethylzinc forms 2 equivalents of the methyl radical.

6.5. Previous Work by Collaborator

The work presented in this section has been performed by Amanda Birgitte Sølvhøj, Ph.D.[125] Following the initial discovery shown in Scheme 61, the solvent was changed to THF and the reaction was measured with GCMS giving a 55 % yield (Table 28, Entry 1). Running the reaction without manganese(II) chloride only afforded 13 % yield. The second improvement when examining the radical alkylation of β-bromostyrene was to change the radical initiator. Using 4-tolylzinc iodide would be expensive in addition to not being atom efficient. Benzoyl peroxide afforded a low yield, 6 %, although manganese(II) chloride improved it to 35 %. Reaction with azobisisobutyronitrile (AIBN) only gave traces of product with and without manganese(II) chloride. Using triethylborane afforded primarily the ethyl radical addition product and only 12 % of the desired compound. Using propylzinc bromide as initiator gave 12 % yield while using zinc chloride did not result in any reaction. Using dimethylzinc resulted in 45 % yield under an air atmosphere and this result increased to 65 % when 30 % manganese(II) chloride was used. Changing the radical initiator and additive loading showed 10 % manganese(II) chloride was enough to enhance the reaction, while 3 equivalents of dimethylzinc was necessary. Various transition metals and sodium chloride were screened as additives, but only manganese(III) acetate and cobalt(II) chloride gave a comparable yield. Manganese(III) acetate, known from its oxidation chemistry, was more expensive than manganese(II) chloride and cobalt(II) chloride was both more toxic and expensive. For this reason manganese(II) chloride was selected for general use.[125] The reactions are shown in Table 28.

Table 28: Optimization of α-alkenylation of THF.[125]



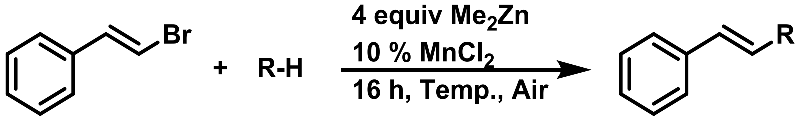
Entry	Initiator	X	Additive	Y	Yield[a]
1[b]	4-MePhZnI	2	$MnCl_2$	30 %	55 %
2[b]	4-MePhZnI	2	-	-	13 %
3[b]	Bz_2O_2	3	-	-	6 %
4	Bz_2O_2	3	$MnCl_2$	12 %	35 %
5[b]	AIBN	3	-	-	Traces
6[b]	AIBN	3	$MnCl_2$	30 %	Traces
7[b]	Et_3B	3	-	-	12 %[c]
8[b]	$ZnCl_2$	2	$MnCl_2$	25 %	-
9[b]	PrZnBr	2	$MnCl_2$	30 %	11 %
10[b]	Et_2Zn	3	$MnCl_2$	30 %	5 %[c]
11[d]	Me_2Zn	3	-	-	33 %
12	Me_2Zn	3	-	-	45 %
13	Me_2Zn	3	$MnCl_2$	30 %	67 %
14	Me_2Zn	2	$MnCl_2$	40 %	56 %
15	Me_2Zn	1.5	$MnCl_2$	35 %	31 %
16	Me_2Zn	1	$MnCl_2$	35 %	31 %
17	Me_2Zn	3	$MnCl_2$	10 %	71-79 %
18	Me_2Zn	3	$MnBr_2$	10 %	62 %
19	Me_2Zn	3	$Mn(OAc)_2$	10 %	43 %
20	Me_2Zn	3	$Mn(OAc)_3$	10 %	75 %
21	Me_2Zn	3	$MnBr(CO)_5$	10 %	58 %
22	Me_2Zn	3	$Mn_2(CO)_{10}$	10 %	60 %
23	Me_2Zn	3	$FeCl_2 \bullet 4H_2O$	30 %	21 %
24	Me_2Zn	3	$FeCl_3$	30 %	28 %
25	Me_2Zn	3	$CuCl_2$	10 %	49 %
26	Me_2Zn	3	$CoCl_2$	10 %	73 %
27	Me_2Zn	3	$CrCl_2$	20 %	62 %
28	Me_2Zn	3	NaCl	20 %	28 %

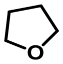
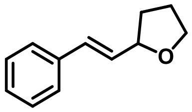
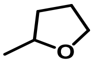
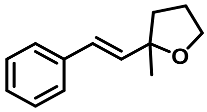
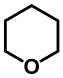
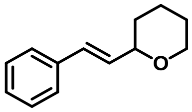
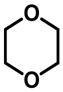
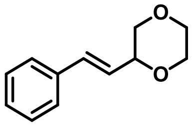
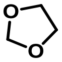
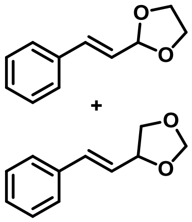
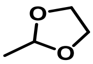
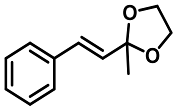
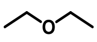
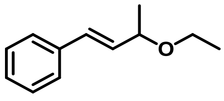
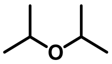
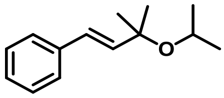
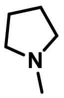
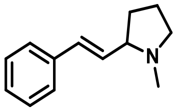
a) GCMS yield.
b) Under argon.
c) Major product was 1-phenylbut-1-ene
d) Performed at room temperature.

With the optimized conditions, a number of cyclic and linear ethers were screened. The reactions are shown in Table 29. In order to isolate and identify the products from the screening reactions the scale was increased to the double. This up-scaling resulted in a decreased yield in the reaction with tetrahydrofuran of 33 %. To increase this yield 4 equivalents of the initiator was used which gave 47 % yield (Table 29, Entry 1). Reaction with 2-methyltetrahydrofuran gave 65 % of (*E*)-2-methyl-2-styryltetrahydrofuran (Entry 2). The GCMS also revealed two smaller product peaks of similar size. The reaction with tetrahydropyran (THP) gave three peaks and the larger was isolated to give (*E*)-2-styryltetrahydro-2-H-pyran in 28 % yield. Again, increasing the amount of the radical initiator led to a 40 % isolated yield (Entry 3). The two unidentified isomers could not be separated but were estimated to be around 10 % of the combined yield. The reaction with 1,4-dioxane did not result in complete conversion but gave a 44 % yield (Entry 4). Reaction with 1,3-dioxane gave two products, addition to the 2- and the 4-position in 31 % and 16 % yield, respectively (Entry 5).[125]

Reaction with 2-methyl-1,3-dioxolane gave 34 % yield of the addition product at the 2-position (Entry 6). Only a trace of the product that resulted from the addition to the 4-position was observed. Reaction with diethyl ether gave 67 % yield (Entry 7). Diisopropyl ether was expected to be a better substrate, but only gave 12 % yield (Entry 8). Finally, reaction with 1-methyl-pyrrolidine gave 71 % yield (Entry 9).[125]

Table 29: Screening of the reaction scope.[125]



Entry	Temperature (C^0)	R-H	Products	Yield (%)
1	65			47
2^b	78			65
3	88			40
4	100			44
5	74			31 + 16
6^b	82			34
7	35			67
8	68			12
9	80			71

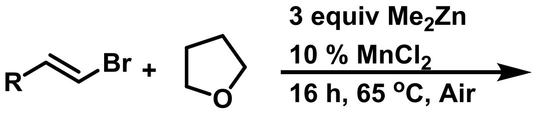
a) Isolated yields
b) 3 equiv. of Me_2Zn were used.

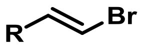
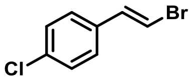
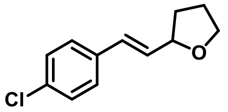
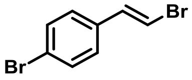
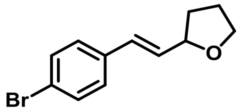
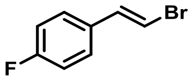
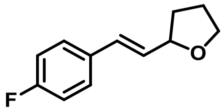
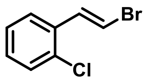
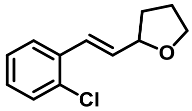
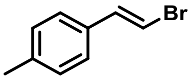
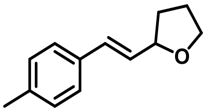
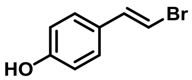
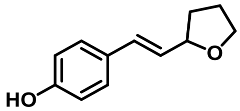
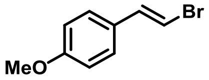
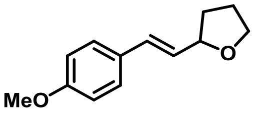
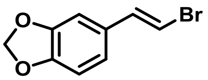
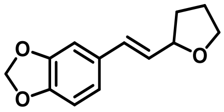
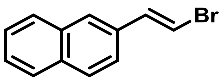
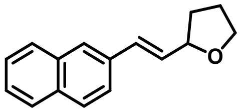
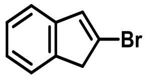
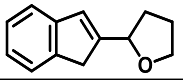
The radical acceptor was also screened for the reaction. Few β-bromostyrenes were commercially available while others were synthesized from readily available cinnamic acids by a previously reported Hunsdiecker[215] reaction. Details on the synthesis of β-bromostyrenes can be found in the experimental data section as they were prepared by the author of this thesis. The reactions with 4-chloro- and 4-bromo-β-bromostyrene both gave 48 % yield (Table 30, Entry 1 and 2). The reaction with 4-fluoro-β-bromostyrene (Entry 3) gave 40 % yield. Using 2-chloro-β-bromostyrene resulted in 54 % yield (Entry 4). The reaction with 4-methyl-β-bromostyrene gave 39 % yield. Reaction with 4-hydroxy- and 4-methoxy-β-bromostyrene gave 39 % and 37 % (Entry 5 and 6) of the desired product, respectively, while reaction with 3,4-methylenedioxy-β-bromostyrene gave 54 % yield (Entry 7).[125]

Since 3 equivalents of dimethylzinc were used for these reactions, they should be compared with the similar reaction for β-bromostyrene which gave 33 % yield. Hence, all reactions gave an improved yield, although the 4-methyl-, 4-hydroxy- and 4-methoxy groups gave close to comparable yield. The electron withdrawing halogen substituents improved yields and comparison with stronger electron withdrawing groups would have been relevant. The reaction with 4-nitro-β-bromostyrene (not shown in table) did not result in any product.[125]

Finally, the reactions with (*E*)-2-(2-bromovinyl)naphthalene and 2-bromoindene gave 21 % and 18 % yield, respectively (Entry 9 and 10). Both needed a additional 3 equivalents of dimethylzinc to obtain a full conversion. In addition to the isolated (E)-2-(2-(naphthalen-2-yl)vinyl)tetrahydrofuran the GCMS indicated several other products, two of which were the addition products of tetrahydrofuranyl (302 m/z) and bromide (312 m/z) without elimination of the bromide. With 2-bromoindene there was no byproduct observed and 28 % of the starting material was recovered. The slower product formation may be attributed to the increased steric hindrance at the 2-position.[125]

Table 30: Scope of the styryl moiety.[125]



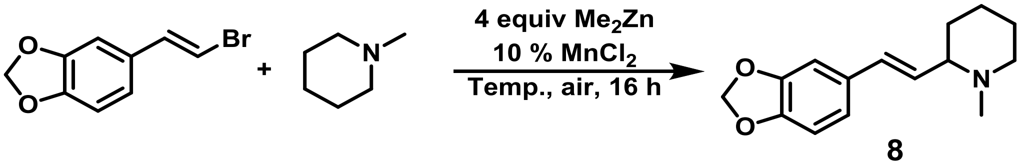
Entry		Product[a]	Yield (%)
1			48
2			48
3			40
4[b]			54
5			39
6[c]			39
7[c]			37
8			54
9[d]			21
10[b, d]			18

a) Isolated yield.
b) 3 days reaction time.
c) 2 days reaction time.
d) Additional 3 equiv. of Me$_2$Zn and 10 % MnCl$_2$ were added after 16 h, followed by 16 h additional reaction time.

6.6. Results

Because the reaction has worked well with methylpyrrolidine, further examination of the coupling with amines was carried out. The first reaction with β-bromostyrene and *N*-ethylpiperidine at 85 ^{o}C gave two inseparable compounds. In order to examine the reaction, 3,4-methylenedioxy-β-bromostyrene was chosen for the optimization because of the higher polarity allowed for better column separation. The reactions are shown in Table 31. At -20 ^{o}C there was no reaction (Table 31, Entry 1), while the yield was 51 % at 0 ^{o}C (Entry 2). At room temperature the yield was 67 % (Entry 3), while the *N*-(3,4-methylenedioxycinnamyl)piperidine side product was isolated in 18 % yield (Entry 4-6). Reactions at 40, 55 and 65 ^{o}C gave 60 %, 77 % and 83 % of the product, respectively. A further increase of the temperature resulted in a lower product yield with 66 % yield at 75 ^{o}C (Entry 7) and a mere 15 % at 85 ^{o}C (Entry 8). At 95 ^{o}C the reaction did not occur (Entry 9). Using a solvent for the reaction was attempted with benzene, heptane and pyridine resulting in 20 %, 18 % and 26 % yield, respectively (Entry 10-12).

Table 31: Optimization of α-alkenylation of tertiary amines.



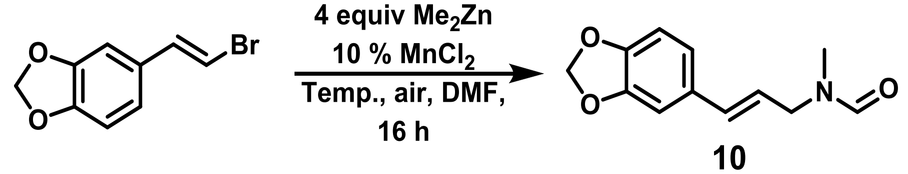
8

Entry	Temperature	Solvent	Yield ([a])
1	-20	neat	-
2	0	neat	51 % (6 %)
3	rt	neat	67 % (18 %)
4	40	neat	60 % (11 %)
5	55	neat	77 %
6	65	neat	83 %
7	75	neat	66 % (8 %)
8	85	neat	15 %
9	95	neat	-
10	65	benzene	20 %
11	65	heptane	18 %
12	65	pyridine	26 %

a) Yield of *N*-(3,4-methylenedioxycinnamyl)piperidine **9** in parenthesis.

Dimethylformamide was used as an electrophile in the reaction since it would have resulted in an interesting building block. Reaction at room temperature gave 15 % yield (Table 32, Entry 1). Increasing the temperature to 65, 85 and 95 ^{0}C gave 19 %, 22 % and 15 % yield, respectively (Entry 2-4). Increasing the reaction time to 3 days resulted in a lower yield of 13 % (Entry 5). Attempts with diethylzinc as the radical initiator resulted in 13 % yield (Entry 6). Since the longer reaction time resulted in a decreased yield, it was possible that the product had degraded. For this reason, the reaction was performed in 2 hours. This reaction resulted in a 5 % yield (Entry 7). These reactions are shown in Table 32.

Table 32: Optimization of α-alkenylation of dimethylformamide.



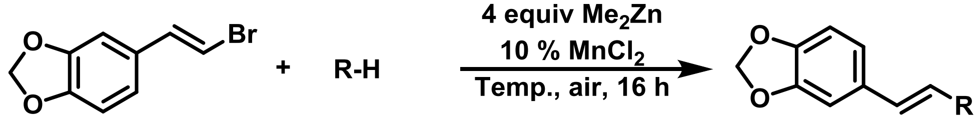
10

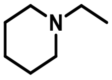
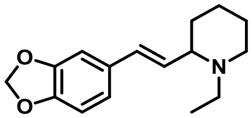
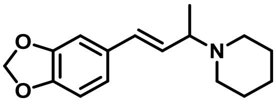
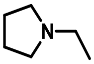
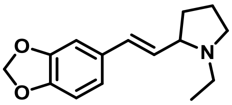
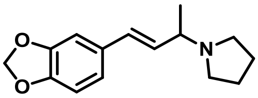
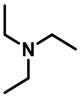
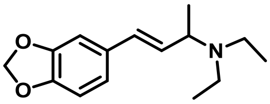
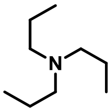
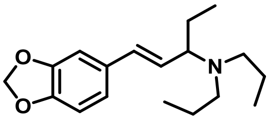
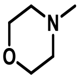
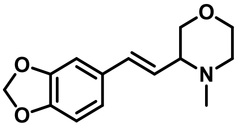
Entry	Temperature	Yield %
1	rt	15
2	65	19
3	85	22
4	95	15
5	65[a]	13
6	65[b]	13
7	65[c]	5

a) 3 days reaction time.
b) Et_2Zn as initiator.
c) 2 hour reaction time, 1 equiv. initiator.

The reaction was attempted with *N*-methyl-indole, *N*-methylpyrrole, pyrrolidine, pyridine and benzyl amine but no product was observed. These reactions are not shown. When dimethylzinc was added to the reactions with pyrrolidine and benzyl amine, the solution generated a colorless precipitate possibly from the formation of methylzinc amine. When *N*-ethylpiperidine was used at 65 ^{o}C, it resulted in 58 % yield of the product. However, the addition to the 2-position on the ethyl group also occoured in 26 % yield. When the temperature was raised to 85 ^{o}C the yield dropped to 22 %, while the side reaction gave 31 % yield (Table 33, Entry 1). The reaction with *N*-ethylpyrrolidine gave 62 % yield of the product and 23 % yield of the byproduct resulting from addition to the 2-position on the ethyl chain (Entry 2). When triethylamine was used at 95 ^{o}C, 95 % yield of the product was isolated (Entry 3). Using tri-*n*-propylamine at 95 ^{o}C gave only 4 % yield and lowering the temperature to 65 ^{o}C increased the yield to 21 % yield. Addition of dimethylzinc at room temperature and raising the temperature to 95 ^{o}C resulted in 17 % yield (Entry 4). Finally, *N*-methylmorpholine was used in the reaction at 65 ^{o}C. TLC and ^{1}H NMR of the crude indicated the formation of three compounds of which only the product of the addition to the 3-position could be isolated, resulting in a 25 % yield (Entry 5).

Table 33: Scope of styrene alkylation.



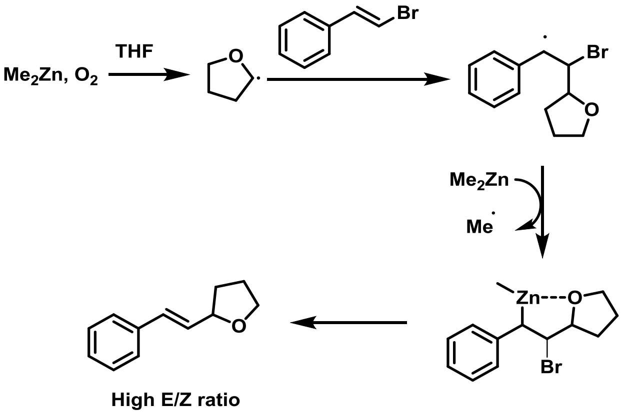
Entry	Temperature (C^o)	R-H	Products[a]
1	65 85		 +  **11** 58 % 22 % **12** 26 % 31 %
2	65		 +  **13** 62 % **14** 23 %
3	95		 **15** 95 %
4	95 65 rt → 95		 **16** 4 % 21 % 17 %
5	65		 **17** 25 %

a) isolated yields.

6.7. Discussion

The reaction mechanism is suggested to be similar to that proposed by Chen *et al.*[199] Oxygen is needed to form the radical from dimethylzinc and the radical extracts the hydrogen from the lowest energy position on tetrahydrofuran. The resulting 2-

tetrahydrofuranyl radical attacks the β-position of the styrene leading to an alkyl radical with free rotation. Coordination of zinc to the radical and chelation to the oxygen favors the formation of the *trans*-product once the elimination occurs. The mechanism is shown in Scheme 72.



Scheme 72: Suggested mechanism for dimethylzinc mediated alkylation of β-bromostyrenes.

Increasing the manganese loading (Table 28, Entry 13 and 14) lowered the yield. Manganese(III) acetate (Entry 20) and cobalt(II) chloride (Entry 26) gave a comparable yield to manganese(II) chloride, both known as radical reductants. The reaction with manganese(II) chloride (Entry 17) gave nearly twice the amount of product as compared to the example without the manganese salt (Entry 12). The mechanism suggested is reasonable for the reaction without manganese(II) chloride, but how the metal enhances the reaction is unknown.

By observing the αC-H bond dissociation energies[216], shown in Table 34, the reactivity of the ethers can be understood. The reaction with tetrahydrofuran (Table 29, Entry 1) has a slightly higher yield than the reaction with tetrahydropyran (Entry 3), probably due to its lower dissociation energy. 1,4-dioxane (Reaction shown in Entry 4) has a higher dissociation energy which results in incomplete conversion. However, because it has twice the reaction sites the yield is still higher than that of tetrahydropyran (Entry 3). Finally, the dissociation energies of the 2- and the 4-position of 1,3-dioxolane are close and thus lead to a mixture of both products (Entry 5).

Table 34: BDE by Shtarev *et al.*[216]

BDE for α-C-H bonds	BDE (kcal/mol)
Tetrahydrofuran (THF)	89.8
Tetrahydropyran (THP)	92.1
1,4-dioxane	93.2
1,3-dioxolane (2-position)	90.0
1,3-dioxolane (4-position)	91.5

The bond dissociation energy of the α-C-H in triethylamine is 90.7 kcal/mol,[217] a value close to that of the α-C-H in tetrahydrofuran. The increased yield compared to the reaction with tetrahydrofuran (Table 30, Entry 8), 54 % yield, can be attributed to the increased reaction temperature. However, reaction with neither 1-methylpiperidine nor tripropylamine worked at this elevated temperature. *N*-Methylpiperidine had a wide temperature range, 0 – 75 ^{o}C (Entry 2-7), where the reaction gave a reasonable yield, down to 51 %. *N*-ethylpiperidine and *N*-ethylpyrrolidine (Table 33, Entry 1 and 2) gave yields slightly lower than *N*-methylpiperidine, 58 % and 62 %, respectively. This can likely be attributed to the longer sidechains that improved stabilization of the radical. The yields of the product and the side product for both reactions are comparable to the reaction with *N*-methylpiperidine at 65 ^{o}C, indicating that only the selectivity for the reaction has changed. Tripropylamine gave a poor yield likely due to steric hindrance.

The manganese catalyzed Negishi cross-coupling was not found in the literature. The fact that the reaction with 4-tolylzinc iodide (Table 28, Entry 1) gave the coupling with THF, only shows that the conditions and substrates were not optimal. To avoid a radical addition-elimination side reaction the alkene moiety can be removed by using an aryl halide as an electrophile instead. The reaction with manganese(II) chloride (Entry 1) gave a considerably higher yield, 55 %, as compared to the one without catalyst, 13 % yield (Entry 2) and this is either due to an improved formation or reactivity of the radical or stabilization of an intermediate. If it is due to an improved reactivity, there will be an increased risk of radical side reactions. The formation of organomanganese compounds is known by using Grignard and organolithium reagents,[137] but a literature search did not reveal any organozinc halides able to perform the same transformation. Even if this should be possible, the resulting organomanganese species are no more likely to perform the oxidative addition of an aryl halide than the corresponding species created from a Grignard reagent.

6.8. Conclusion

A new dimethylzinc initiated radical coupling of ethers and tertiary amines with β-bromostyrene was developed and the reaction scope was examined. Like other radical reactions, the reactivity is dependent on the bond strengths of the pre-radical nucleophile and steric hindrance. The products with *Z*-configuration is known from similar reaction with dimethylzinc and suggested to be due to a chelation effect.

6.9. Experimental Data

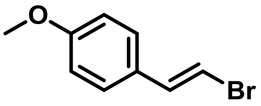
General Method

Flash column chromatography separations were performed on silica gel 60 (40 – 63 μm). NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.16 ppm).[177] HRMS measurements where made using ESI with TOF detection.

General Method A: synthesis of 2-bromovinylbenzenes

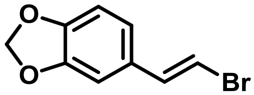
The procedure was based on the synthesis of 2-bromovinylbenzenes with the manganese catalyzed Hunsdiecker described by Chowdhury and Roy[215]. Cinnamic acid (1 equiv), *N*-bromosuccinimide (1 equiv) and $Mn(OAc)_2$ (10 mol%) were stirred overnight in 1:1 acetonitrile/H_2O at rt. The solution was extracted with dichloromethane and concentrated on Celite. Flash column chromatography gave the desired product.

(*E*)-1-(2-Bromovinyl)-4-methoxybenzene



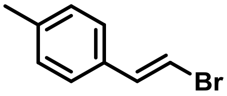
Using general method A, 4-methoxycinnamic acid (2.7 g, 15 mmol) was mixed with *N*-bromosuccinimide (2.7 g, 15 mmol) and $Mn(OAc)_2$ (0.26 g, 1.5 mmol) in 1:1 acetonitrile/H_2O (50 mL) overnight. The crude was extracted with dichloromethane and concentrated on Celite. Flash column chromatography (pentane) gave 1.432 g (44 % yield) of the desired compound as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.23 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 14.0 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 14.0 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.8, 136.7, 128.9, 127.5, 114.3, 104.1, 55.5. ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[218]

1,2-Methylenedioxy-(*E*)-4-(2-bromovinyl)benzene



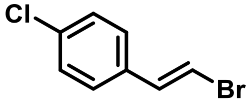
Using general method A, 3,4-methylenedioxycinnamic acid (2.9 g, 15 mmol) was mixed with *N*-bromosuccinimide (2.7 g, 15 mmol) and $Mn(OAc)_2$ (0.26 g, 1.5 mmol) in 1:1 acetonitrile/H_2O (50 mL) overnight. The crude was extracted with dichloromethane and concentrated on Celite. Flash column chromatography (pentane) gave 1.7 g (50 % yield) of the desired compound as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.99 (d, J = 13.9 Hz, 1H), 6.80 (d, J = 1.2 Hz, 1H), 6.77-6.71 (m, 2H), 6.58 (d, J = 13.9 Hz, 1H), 5.95 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.2, 147.8, 136.7, 130.3, 121.0, 108.5, 105.4, 104.6, 101.3. ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[218]

(*E*)-1-(2-Bromovinyl)-4-methylbenzene



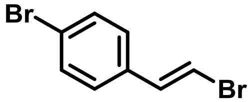
Using general method A, 4-methylcinnamic acid (2.4 g, 15 mmol) was mixed with *N*-bromosuccinimide (2.7 g, 15 mmol) and $Mn(OAc)_2$ (0.26 g, 1.5 mmol) in 1:1 acetonitrile/H_2O (50 mL) overnight. The crude was extracted with dichloromethane and concentrated on Celite. Flash column chromatography (pentane) gave 1.156 g (40 % yield) of the desired compound as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 14 Hz, 1H), 6.71 (d, J = 14 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.4, 137.2, 133.3, 129.6, 126.1, 105.6, 21.4. ^{1}H and ^{13}C NMR spectra were in accordance with those described in the literature.[219]

1-(2-Bromovinyl)-4-chlorobenzene



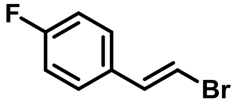
Using general method A, 4-chlorocinnamic acid (2.7 g, 14.8 mmol) was mixed with *N*-bromosuccinimide (2.7 g, 15 mmol), and $Mn(OAc)_2$ (0.26 g, 1.5 mmol) in 1:1 acetonitrile/H_2O (50 mL) overnight. The crude was extracted with dichloromethane and concentrated on Celite. Flash column chromatography (pentane) gave the desired compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30 (d, *J* = 8.60 Hz, 2H), 7.23 (d, *J* = 8.50 Hz, 2H), 7.06 (d, *J* = 14.00 Hz, 1H), 6.77 (d, *J* = 14.00 Hz, 1H). ^1H NMR spectrum was in accordance with that described in the literature.[219] A very weak ^{13}C NMR was not inconsistent with that described in the literature.

(*E*)-1-(2-Bromovinyl)-4-bromobenzene



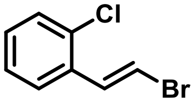
Using general method A, 4-bromocinnamic acid (3.4 g, 15 mmol) was mixed with *N*-bromosuccinimide (2.7 g, 15 mmol) and $Mn(OAc)_2$ (0.26 g, 1.5 mmol) in 1:1 acetonitrile/H_2O (50 mL) overnight. The crude was extracted with dichloromethane and concentrated on Celite. Flash column chromatography (pentane) gave 0.852 g (22 % yield) of the desired compound as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 14.0 Hz, 1H), 6.78 (d, *J* = 14.0 Hz, 1H,). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.2, 135.0, 132.1, 127.7, 122.3, 107.5. ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[218]

(*E*)-1-(2-Bromovinyl)-4-fluorobenzene



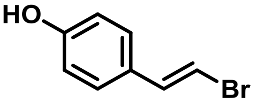
Using general method A, 4-fluorocinnamic acid (2.5 g, 15 mmol) was mixed with *N*-bromosuccinimide (2.7 g, 15 mmol) and $Mn(OAc)_2$ (0.26 g, 1.5 mmol) in 1:1 acetonitrile/H_2O (50 mL) overnight. The crude was extracted with dichloromethane and concentrated on Celite. Flash column chromatography (pentane) gave the desired compound (96:4 E/Z) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (dd, *J* = 5.3, 8.7 Hz, 2H), 7.07 (d, *J* = 14.0 Hz, 1H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 14.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.7 (d, *J* = 246.8 Hz), 136.1, 132.3 (d, *J* = 3.5 Hz), 127.8 (d, *J* = 8.1 Hz), 115.9 (d, *J* = 86.6 Hz), 106.2 (d, *J* = 9.8 Hz). ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[219]

(*E*)-1-(2-Bromovinyl)-2-chlorobenzene



Using general method A, 2-chlorocinnamic acid (2.7 g, 14.8 mmol) was mixed with *N*-bromosuccinimide (2.7 g, 15 mmol) and $Mn(OAc)_2$ (0.26 g, 1.5 mmol) in 1:1 acetonitrile/H_2O (50 mL) overnight. The crude was extracted with dichloromethane and concentrated on Celite. Flash column chromatography (pentane) gave 0.4 g (12 % yield) of the desired compound as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.78 (d, *J* = 14.00 Hz, 1H), 7.39-7.33 (m, 2H), 7.22-7.20 (m, 2H), 6.78 (d, *J* = 14.00 Hz, 1H). ^1H NMR spectrum was in accordance with that described in the literature.[219]

1-(2-Bromovinyl)-4-hydroxybenzene

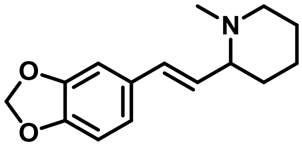


Using general method A, 4-hydroxycinnamic acid (1.56 g, 10 mmol) was mixed with *N*-bromosuccinimide (1.8 g, 10 mmol) and $Mn(OAc)_2$ (0.18 g, 1 mmol) in 1:1 acetonitrile/H_2O (50 mL) overnight. The crude was extracted with dichloromethane and concentrated on Celite. Flash column chromatography (40-100 % CH_2Cl_2:pentane) gave 123 mg (6 % yield) the desired compound as a colorless solid in a ratio of 1:20 Z/E. (*E*)-1-(2-bromovinyl)-4-hydroxybenzene. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.19 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 14 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 14 Hz, 1H), 5.11 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.6, 136.5, 129.2, 127.7, 115.8, 104.3. (*Z*)-1-(2-bromovinyl)-4-hydroxybenzene ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 8.1 Hz, 1H), 5.16 (s, 1H). ^1H and ^{13}C NMR spectra were in accordance with those described in the literature.[220,221]

General Method B: Synthesis of β-styrene derivatives

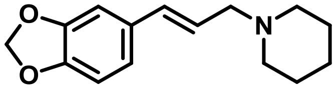
In a 50 mL roundbottom flask equipped with a condenser, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) were dissolved in the tertiary amine (10 mL) and heated to 65 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with saturated sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were concentrated *in vacuo.* The crude product was purified using flash column chromatography.

(*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl)-1-methylpiperidine (8)



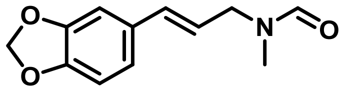
Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in *N*-methylpiperidine (10 mL) and heated to 65 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with saturated sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). After concentration *in vacuo* flash column chromatography (2:98 TEA:heptane) gave the product (204.0 mg, 83 % yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 6.91 (d, *J* = 1.36 Hz, 1H), 6.78 (dd, *J* = 1.42 Hz and 8.02 Hz, 1H), 6.74 (d, *J* = 7.98 Hz, 1H), 6.39 (d, *J* = 15.82 Hz, 1H), 5.97 (dd, *J* = 8.69 Hz and 16.00 Hz, 1H), 5.94 (s, 3H), 2.91 (d, *J* = 11.41 Hz, 1H), 2.46-2.38 (m, 1H), 2.23 (s, 3H), 20.2 (dt, *J* = 3.54 Hz and 11.60 Hz, 1H), 1.75 (dd, *J* = 2.87 Hz and 12.61 Hz, 1H), 1.70-1.53 (m, 3H), 1.52-1.40 (m, 1H), 1.35-1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 148.1, 147.1, 132.1, 131.8, 130.3, 120.8, 108.4, 105.8, 101.1, 68.2, 56.6, 44.8, 33.7, 26.2, 24.1. HRMS cald. for $C_{15}H_{20}NO_2^+$ [MH^+]: 246.1489, found: 246.1490.

(*E*)-1-(3-(Benzo[*d*][1,3]dioxol-5-yl)allyl)piperidine (9)



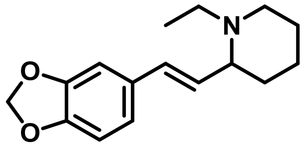
Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in *N*-methylpiperidine (10 mL) and heated to 65 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). After concentration *in vacuo* flash column chromatography (2:98 TEA:heptane) gave the product as an orange solid (20.2 mg, 8 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 6.92 (d, *J* = 1.30 Hz, 1H), 6.83-6.76 (m, 1H), 6.74 (d, *J* = 8.00 Hz, 1H), 6.42 (d, *J* = 15.80 Hz, 1H), 6.15 (dt, *J* = 15.70 Hz, 1H), 5.94 (s, 2H), 3.16 (d, *J* = 6.80 Hz, 2H), 2.50 (br, 4H), 1.76-1.56 (m, 4H), 1.47 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.1, 147.3, 143.5, 133.4, 131.4, 121.1, 108.4, 105.9, 101.2, 61.7, 54.4, 25.6, 24.2. HRMS calcd. for $C_{15}H_{20}NO_2^+$ [MH$^+$]: 246.1489, found: 246.1494.

(*E*)-*N*-(3-(Benzo[*d*][1,3]dioxol-5-yl)allyl)-*N*-methylformamide (10)



Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in *N,N*-dimethylformamide (10 mL) and heated to 85 °C under stirring. Me$_2$Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with sodium hydroxide (10 mL) and extracted with CH$_2$Cl$_2$ (2 x 20 mL). After concentration *in vacuo* flash column chromatography (3:7 heptane/EtOAc) gave the desired compound (49.0 mg, 22 % yield) as a light brown oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) (major rotamer) 8.14 (s, 1H), 6.90 (s, 1H), 6.83-6.71 (m, 2H), 6.45 (d, J = 15.80 Hz, 1H), 6.00-5.83 (m, 3H), 3.95 (d, J = 5.80 Hz, 2H), 2.86 (s, 3H). (minor rotamer) 8.09 (1H, s), 6.90 (s, 1H), 6.83-6.71 (m, 2H), 6.45 (d, J = 15.80 Hz, 1H), 6.00-5.83 (m, 3H,), 4.07 (d, J = 6.50 Hz, 2H), 2.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) (major rotamer), 162.8, 148.3, 147.8, 133.5, 130.5, 122.2, 121.5, 108.5, 105.8, 101.3 (minor rotamer), 162.5, 148.2, 147.6, 133.4, 130.9, 121.6, 121.3, 108.4, 105.8, 101.3. HRMS: calcd for $C_{12}H_{14}NO_3$ 220.0968 [M+H]$^+$; found: 220.0968.

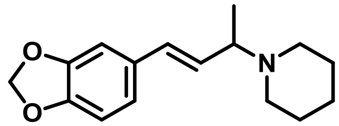
(*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl)-1-ethylpiperidine (11)



Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in *N*-ethylpiperidine (10 mL) and heated to 65 °C under stirring. Me$_2$Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with sodium hydroxide (10 mL) and extracted with CH$_2$Cl$_2$ (2 x 20 mL). After concentration *in vacuo* flash column chromatography (96:3:1 → 95:4:1 heptane:diethyl ether:TEA) gave the product (150.4 mg, 58 % yield) as a brown oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 6.90 (d, J = 1.52 Hz, 1H), 6.77 (dd, J = 1.48 Hz and 8.00 Hz, 1H), 6.73 (d, J = 8.00 Hz, 1H), 6.38 (d, J = 15.84 Hz, 1H), 6.00 (d, J = 15.84 Hz, 1H), 5.92 (s, 2H), 3.00 (dt, J = 3.10 Hz and 11.25 Hz, 1H), 2.85 (dq, J = 7.33 Hz and 14.64 Hz, 1H), 2.75-5.65 (m, 1H), 2.24 (dq, J = 7.00 Hz and 13.90 Hz, 1H), 2.01

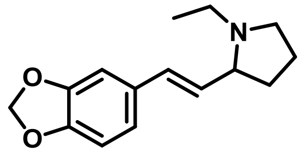
(dt, J = 2.90 Hz and 11.50 Hz, 1H), 1.79-1.41 (m, 5H), 1.37-1.19 (m, 1H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.1, 147.1, 131.8, 131.8, 130.1, 120.8, 108.3, 105.7, 101.1, 65.7, 51.5, 49.4, 33.8, 25.9, 24.0, 10.9. HRMS: calcd for $C_{16}H_{22}NO_2$ 260.1645 $[M+H]^+$; found: 260.1643.

(*E*)-1-(4-(Benzo[*d*][1,3]dioxol-5-yl)but-3-en-2-yl)piperidine (12)



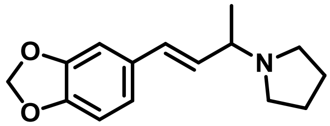
Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in *N*-ethylpiperidine (10 mL) and heated to 85 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). After concentration *in vacuo* flash column chromatography (96:3:1 → 95:4:1 heptane:diethyl ether:TEA) gave the product (86.3 mg, 31 % yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.92 (d, J = 1.44 Hz, 1H), 6.78 (dd, J = 1.52 Hz and 8.04 Hz, 1H), 6.73 (d, J = 8.00 Hz, 1H), 6.33 (d, J = 15.88 Hz, 1H), 6.06 (dd, J = 8.00 Hz and 15.84 Hz, 1H), 5.93 (s, 2H,), 3.09-3.02 (m, 1H), 2.57-2.38 (m, 4H), 1.63-1.57 (4H, m), 1.45-1.41 (2H, m), 1.24 (d, J = 6.60 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.1, 147.1, 131.8, 130.9, 130.3, 120.9, 108.4, 105.7, 101.1, 63.1, 51.1, 26.3, 24.7, 17.8. HRMS: calcd for $C_{16}H_{22}NO_2$ 260.1645 $[M+H]^+$; found: 260.1649.

(*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl)-1-ethylpyrrolidine (13)



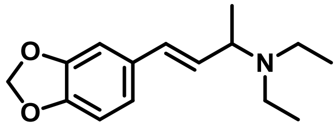
Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in *N*-ethylpyrrolidine (5 mL) and heated to 65 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with saturated sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). After concentration *in vacuo* flash column chromatography (2:98 TEA:heptane) gave the product (151.6 mg, 62 % yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.85 (d, J = 1.57 Hz, 1H), 6.72 (dd, J = 1.55 Hz and 8.02 Hz, 1H), 6.66 (d, J = 7.99, 1H), 6.30 (d, J = 15.74 Hz, 1H), 5.86 (dd, J = 8.40 Hz and 15.60 Hz, 1H), 5.85 (s, 3H), 2.79 (dq, J = 7.45 Hz and 11.98 Hz, 1H), 2.69 (dd, J = 8.41 Hz and 16.11 Hz, 1H), 2.17-1.53 (m, 6H), 1.02 (t, *J* = 7.25 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.1, 147.1, 131.7, 131.1, 130.9, 120.9, 108.3, 105.8, 101.1, 68.6, 53.1, 48.2, 32.0, 22.2, 13.9. HRMS: calcd for $C_{16}H_{20}NO_2$ 246.1489 $[M+H]^+$; found: 246.1492.

(*E*)-1-(4-(Benzo[*d*][1,3]dioxol-5-yl)but-3-en-2-yl)pyrrolidine (14)



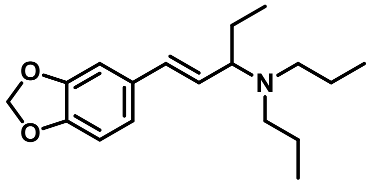
Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in *N*-ethylpyrrolidine (5 mL) and heated to 65 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). After concentration *in vacuo* flash column chromatography (2:98 TEA:heptane) gave the product (56.8 mg, 23 % yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.84 (d, *J* = 1.42 Hz, 1H), 6.71 (dd, *J* = 1.48 Hz and 8.03 Hz, 1H), 6.67 (d, *J* = 7.99 Hz, 1H), 6.30 (d, *J* = 15.78 Hz, 1H), 5.98 (dd, *J* = 8.52 Hz and 15.78 Hz, 1H), 5.86 (s, 2H), 2.79 (dq, *J* = 6.44 Hz and 13.01 Hz, 1H), 2.58-2.40 (m, 4H), 2.00-1.57 (m, 4H), 1.20 (d, *J* = 6.45 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.1, 147.1, 132.5, 131.9, 129.3, 120.9, 108.4, 105.8, 101.1, 63.1, 52.4, 23.5, 21.2. HRMS: calcd for $C_{16}H_{20}NO_2$ 246.1489 $[M+H]^+$; found: 246.1486.

(*E*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-*N*,*N*-diethylbut-3-en-2-amine (15)



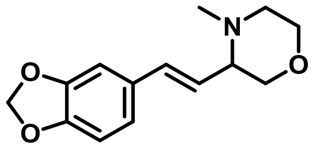
Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in TEA (10 mL) and heated to 65 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with saturated sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). After concentration *in vacuo* flash column chromatography (1 % TEA in heptane) gave the desired compound (240.6 mg, 95 % yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.92 (d, *J* = 1.52 Hz, 1H), 6.79 (dd, *J* = 1.52 Hz and 8.04 Hz, 1H), 6.74 (d, *J* = 8.00 Hz, 1H), 6.34 (d, *J* = 15.88 Hz, 1H), 6.05 (dd, *J* = 7.44 Hz and 15.92 Hz, 1H), 5.93 (s, 2H), 3.45-3.39 (m, 1H), 2.66-2.50 (m, 4H), 1.21 (d, *J* = 6.64 Hz, 3H), 1.04 (t, *J* = 7.12 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.1, 147.0, 132.1, 131.7, 129.6, 120.8, 108.4, 105.7, 101.1, 57.5, 43.6, 17.6, 13.2. HRMS: calcd for $C_{15}H_{20}NO_2$ 246.1645 $[M+H]^+$; found: 248.1646.

(*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-*N*,*N*-dipropylpent-1-en-3-amine (16)



Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in tripropylamine (10 mL) and heated to 65 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with saturated sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). After concentration *in vacuo* flash column chromatography (20:80 ether:heptane) gave the product (60.2 mg, 21 % yield) as a light brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.93 (d, *J* = 1.40 Hz, 1H), 6.79 (dd, *J* = 1.42 Hz and 8.02 Hz, 1H), 6.75 (d, *J* = 8.00 Hz, 1H), 6.30 (d, *J* = 15.80 Hz, 1H), 5.96 (dd, *J* = 8.70 Hz and 16.00 Hz, 1H), 5.94 (s, 2H), 2.99 (td, *J* = 6.30 Hz and 8.30 Hz, 1H), 2.48 (ddd, *J* = 7.00 Hz, 8.80 Hz and 12.90 Hz, 2H), 2.38-2.28 (m, 2H), 1.65 (m, 1H), 1.54-1.35 (m, 5H), 0.92-0.85 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 148.1, 146.9, 132.2, 131.3, 128.6, 120.8, 108.4, 105.7, 101.1, 65.1, 52.8, 25.9, 22.0, 12.1, 11.6. HRMS: calcd for $C_{18}H_{28}NO_2$ 290.2115 $[M+H]^+$; found: 290.2110.

(*E*)-3-(2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl)-4-methylmorpholine (17)



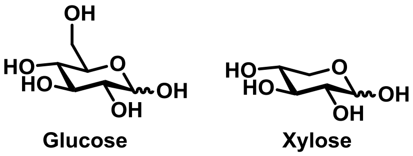
Using general method B, 3,4-(methylenedioxy)-β-bromostyrene (1 mmol) and manganese (II) chloride (0.1 mmol) was dissolved in *N*-methylmorpholine (10 mL) and heated to 65 °C under stirring. Me_2Zn 1 M in hexane (4 mmol) was added and the reaction was left overnight. The reaction was treated with saturated sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). After concentration *in vacuo* flash column chromatography (20:79:1 toluene:ether:TEA) gave the product (62.2 mg, 25 % yield) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 6.91 (d, *J* = 1.35 Hz, 1H), 6.80 (dd, *J* = 1.43 Hz and 8.03 Hz, 1H), 6.75 (d, *J* = 7.99 hz, 1H), 6.53 (d, *J* = 15.90 Hz, 1H), 5.95 (s, 2H), 5.83 (dd, *J* = 8.71 Hz and 15.88 Hz, 1H), 3.86 (d, *J* = 11.41 Hz, 1H), 3.79-3.67 (m, 2H), 3.42 (t, *J* = 10.63 Hz, 1H), 2.82-2.75 (m, 2H), 2.37 (dt, *J* = 3.23 Hz and 11.60 Hz, 1H), 2.30 (s, 3H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ (ppm) 148.2, 147.6, 134.1, 131.0, 124.1, 121.3, 108.4, 105.8, 101.3, 71.1, 67.3, 66.7, 54.8, 43.7. HRMS: calcd for $C_{14}H_{18}NO_3$ 248.1281 $[M+H]^+$; found: 248.1283.

Appendix A: Zeolite-Catalyzed Degradation of Sugars

One of contemporary society's challenges in chemistry is to handle the transition from fossil-based raw materials to renewable and less greenhouse gas producing alternatives. Fossil based materials are not only the world's main energy source, about 75 %,[222] but also industrial chemicals and materials are mainly derived from non-renewable sources. The energy needs might be filled by combinations of non-carbon based means such as electricity from solar, water, wind and nuclear power in addition to the carbon based option of burning fuel from biomass.[223] To fill the need for chemicals though, an economical, energy-efficient and sustainable production of chemicals from plant biomass is the only current option.[224] The interest in decreasing the dependence on fossil-based raw materials have directed researchers attention to identifying new sources for chemicals and for finding novel products with improved properties to replace the existing chemicals. Meanwhile there is the added benefit of perhaps finding chemicals with entirely new applications.[225]

Biomass consists primarily of cellulose, which is a polymer of glucose; hemicellulose, which is a polymer of mostly glucose and xylose; in addition to lignin; which is a cross-linked polymer made of substituted phenols, that together make the plant rigid.



Scheme 73: Primary carbohydrates in biomass

In addition, the plant stores energy in the form of lipids, sugars and starch, another polymer of glucose, as well as other products such as terpenes.[225] From natures annual production of biomass, around 170 billion metric tons in total, 75 % is estimated to be carbohydrates, and of this 3-4 % is used by humans.[225] Transformation of biomass into chemicals is done by both fermentation and by chemical processes.[225] The ability to operate at low temperature has made biochemical processes more applicable than the chemical counterparts due to the thermal instability of carbohydrates. Developing chemical catalytic processes on the other hand would be attractive, since they often result in better process control, scalability, cheaper product workup and overall higher productivity.[226] Heterogeneous catalysts have been efficient for the chemical transformation of fossil resources to fuel and chemicals, but the scope of their use in biomass processes is not yet clear. One class of heterogeneous catalysts that shows such promise is zeolites.[227] Zeolites are a contraction of “zeo” and “lithos” meaning “boil” and “stone” as it was named in 1756 by Cronstedt after he had discovered that some silicate minerals could swell and fuse when heated.[228] They are composed by SiO_4 and $[AlO_4]^-$ tetrahedra together with the cation to balance the charge, forming a crystalline microporous material that are excellent for recognizing, discriminating and organizing molecules with high precision. Their already established success in industrial catalysis of fossil based materials, such as fluid catalytic cracking (FCC), which cracks larger hydrocarbon molecules into smaller gasoline classified ones and methanol to gasoline (MTG), is caused by a combination of these properties. A zeolite has, due to its porous structure, a high surface area and an adsorption capacity that can be controlled, based on the synthesis of the zeolite. The zeolite can be hydrophilic or hydrophobic and the active sites can be tailored for a particular application, such as the strength and concentration of the acid sites while the size of the channels and cavities have an optimal size for many molecules of interest. In addition, there is a pre-activation of molecules inside the zeolite due to an electronic confinement together with a strong electric field due to the organization of partial charges caused by the ion framework. About 40 naturally occurring zeolites have been discovered while the synthetic analogues count for approximately 75 different structure types alone. The classification is based on the tetrahedral atoms connectivity from the maximum topological symmetry and each structure is assigned a three letter code.[227–230] For example, the work presented in this appendix was carried out with catalysis using the zeolite Sn-Beta. The beta zeolite has the framework designated BEA which is formed from the composite building units mor, bea and mtw, the idealized structure is shown in Figure 2.

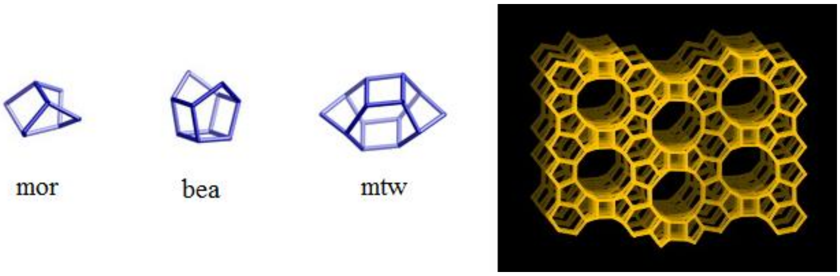
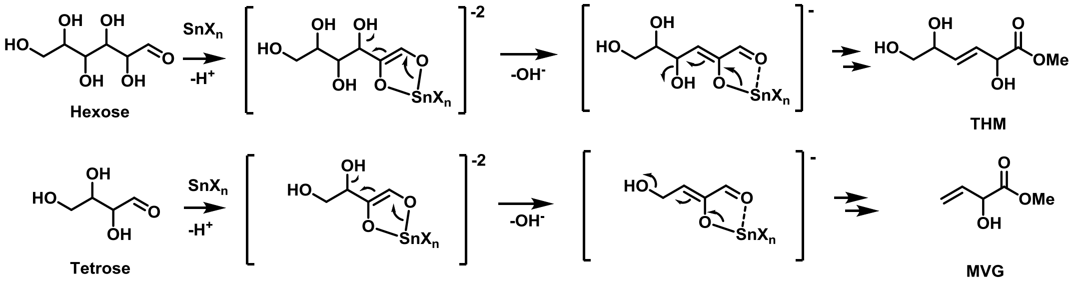


Figure 2: Composite building blocks and framework view adapted from Database of Zeolite Structures.[231]

The Sn-betas 12-atom ring pores allows for a 5.95 Å sphere to pass through along all three axes.[231]

Holm *et al.*[226] from Haldor Topsøe A/S discovered Sn-Beta ability to catalyze the direct formation of methyl lactate from hexoses and disaccharides of hexoses. The derivative lactic acid is primarily used in the food industry and its application ranges from use in the leather tanning industry, pharmaceutical and cosmetic applications, to the production of poly(lactic acid) (PLA) as a bio-degradable plastic and solvents.[232] A fermentation process already exists where lactic acid is made from glucose. However this method results in large amounts of waste salts being produced leaving much room for improvement. In this process methyl lactate can be purified by distillation. Unfortunately, the process results in a racemic mixture of products making it less usable for plastic production. The largest byproduct was methyl vinyl glycolate (methyl 2-hydroxy-3-butenoate) or MVG which was found to be the main product, if the reaction was performed with D-erythrose. In the reaction with glucose, shorter reaction times could be achieved with the addition of alkali metal salts, but when they were omitted, a greater number of possible side products were revealed.[226] It was found that Sn-beta could form *trans*-2,5,6-trihydroxy-3-hexenoic acid methyl ester (THM) from hexoses.[233] The proposed mechanism for the formation of both THM and MVG with tin is shown in Scheme 74.

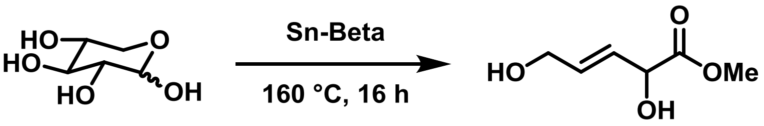

Scheme 74: Proposed mechanism for the formation of THM and MVG respectively.[234,235]

The reaction of glucose with Sn-Beta in the presence of K_2CO_3 results in about 50 % methyl lactate and about 18 % MVG. MVG can be used as copolymer in PLA to tune its properties together, as well as serve as a starting compound for a number of other chemicals.[236]

With glucose as the most abundant monosaccharide in nature the search for usable chemicals by stannosilicate catalysis started here. The five-carbon and second most abundant monosaccharide, xylose, was also examined. Currently xylitol, furfural and lactic acid are products from xylose feedstock, but any additional high-value products would strengthen the biorefinery industry. Reaction with xylose at 160 °C with Sn-Beta in methanol gave 32 % of *trans*-2,5-dihydroxy-3-pentenoic acid methyl ester, DPM, the five-carbon homologue to MVG and THM, along with a number of previously seen byproducts. Subsequent polymerization of DPM with ethyl 6-hydroxyhexanoate as a copolymer was successful, giving access to a more functionalized polymer than poly(ε-caprolactone) (the polymer of ethyl 6-hydroxyhexanoate), while it was expected that the biodegradability properties would remain. The polymer was functionalized with trifluoroacetic anhydride, TFAA, and a number of thiols using 2,2-dimethyoxy-2-phenylacetophenone, DMPA, and UV-light.[237] With these results, it was decided that a more comprehensive study of the possibilities of DPM was prudent. To do this, DPM was needed in gram scale quantities and the project described below was started with the goal of producing 100 g of DPM.

Results and Discussion

The following work was carried out during an external stay at Haldor Topsøe A/S. Without access to previous upscaling conditions,[237] initial experiments were concentrated in an attempt to increase the amount of the product. The reaction conditions are presented in Scheme 75.

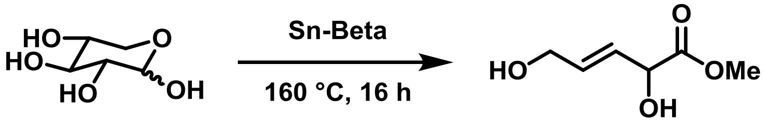


Conditions: 60 g D-xylose, 30 g Sn-Beta and 300 g methanol in autoclave at 160 °C for 16 hours.

Scheme 75: Conditions for formation of DPM.

The Sn-Beta used initially had a shape of small cylinders, but after use and subsequent regeneration by calcination it had various shapes and sizes and should be grinded carefully before use. The total number of experiments performed was 21, where 15 of them were carried out on the 60 g scale, as shown in Scheme 75 and 8 were performed in a smaller autoclave on a 3 g scale. Unfortunately, many results were non-usable since the difference in catalytic effect of grinded versus non-grinded reused catalyst was discovered too late. Likewise, several experiments are omitted at the request of Haldor Topsøe. The experiments on a small scale were carried out with 3 g of D-xylose, 1.5 g of Sn-Beta in 15 g methanol at 160 °C, i.e. the concentration of xylose and Sn-Beta was twice that on the larger scale. Selected 3 g scale reactions are shown in Table 35.

Table 35: Small scale production of DPM.



Entry[a]	Time (h)	Concentration (g/L)[b]
1[c]	1	22.7
2[d]	4	25.5
3[c]	16	23.6

a) Conditions: 3 g D-xylose, 1.5 g Sn-Beta in 15 g methanol at 160 °C. The crude was filtered by suction and a sample was taken from the crude and filtered through a syringe filter before submitted to GC-FID

b) Concentration were based on previous calibrated peaks.

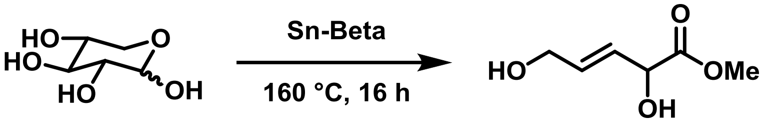
c) New catalyst.

d) Regenerated, non-grinded catalyst.

The first reaction was carried out with new catalyst and ran for 4 hours (Table 35, Entry 2) and gave a concentration of 25.5 g/L on a previously calibrated gas chromatograph with flame ionization detection. Experiments at 1 and 16 hours was carried out but gave a comparable concentration of product (Entry 1 and 3).

The small-scale reactions were performed alongside the large-scale reactions and the condition of the catalyst used was carefully noted from then on. At this time, however the focus shifted and the purification of the crude reaction mixtures became the focus, as originally planned. This meant that the reaction experiments were discontinued on the small scale and optimization of the reaction time for the larger scale was never performed, since it would take time from purification attempts. The larger scale reactions are shown in Table 36.

Table 36: Large scale production of DPM.



Entry	Catalyst	Est. Yield[a] (g)
1[b]	New	9.4
2	New	9.6
3	new	11.1
4	new	9.4
5	reused	10.7
6	New	9.3
7	New	10.1
8[c]	reused	10.5

a) Conditions: 60 g D-xylose, 30 g Sn-Beta and 300 g methanol in autoclave at 160 °C for 16 hours. Crude was filtered with suction and a sample was filtered with syringe and measured on a precalibrated GC-FID.
b) The yield is the GC-FID estimated concentration times the volume of the crude.
c) Kevlar lining blew on the autoclave after 1 hour of reaction time.
d) Only 200 g methanol was used in the reaction.

The first reaction (Table 36, Entry 1) ran for about an hour before the Kevlar lining blew and the reaction had to be stopped. It took several hours for it to cool and afterwards much of the methanol had evaporated. When this reaction was compared to the second reaction (Entry 2) that had the same conditions but was performed over 16 hours, now with a metal ring lining, the estimated yields were comparable. This result was similar to the small-scale reactions comparing 1 and 16 hours (Table 35, Entry 1 and 3) also with a comparable concentration. To clarify the role of the new vs the reused catalyst the reactions were repeated. Four experiments with new catalyst (Entry 3, 4, 6 and 7) gave an estimated yield ranging from 9.3 g to 11.1 g. An experiment using reused grinded catalyst (Entry 5) gave an estimated yield of 10.7 g. The reaction was performed with reused catalyst and with only 200 g methanol as solvent (Entry 8). This gave an estimated yield of 10.5 g, showing the reaction was not strongly influenced by the substrate concentration. Two more reactions were performed, both using reused grinded catalyst, and one of them using 45 g of Sn-Beta, but due to external factors it was not possible to follow the normal post-autoclave procedure. They both gave considerably less yield than previous reactions. At this point, the total amount of DPM in the crude mixtures was estimated to be around 150 g and production was discontinued. The reaction yields from 9.3 g to 11.8 g correspond to 20 – 25 % yield. Normally yields within such a small percentage difference are considered comparable and it could be argued that all experiments carried out on a 60 g scale had the same result, regardless of the catalyst conditions. In addition, to emphasize this, the reaction with the lowest yield and the reaction with the second highest yield were carried out under the same conditions.

Previously, purification has been done by Dry Column Vacuum Chromatography, DCVC. Using this method would require around 1 L of solvent. A detailed description of the purification method is left out at the request of Haldor Topsøe. However, an overloaded DCVC column was attempted. Using ten times the optimal loading, this still required around one fourth of the solvent necessary for a non-overloaded DCVC column and only removed some impurities. Of the estimated 150 g of DPM in the mixture, 70 g was isolated with some impurities. Two DCVC columns with 20 g distilled DPM were performed, giving around 10 g of relatively pure DPM each and 20 g of DPM with concentrated impurities.

Conclusion

The goal of the project was to produce 100 g of DPM. Only 70 g was produced of varying purity. The large-scale reactions gave comparable yields, regardless of whether new or reused catalyst was used. The condition of the reused catalyst might have some impact, i.e. using lumpy Sn-Beta might reduce the yield while grinded reused Sn-Beta performs comparable to new Sn-Beta. Due to external factors and time constraints, no optimization was performed on the large-scale reaction. Previous work up and purification methods were found inadequate when working with the large-scale reactions and another method was necessary to handle the larger quantities.

Appendix B. Abbreviations

AIBN	Azobisisobutyronitrile
BDE	Bond dissociation energy
BHT	Butylated hydroxytoluene
C	Celcius
DABCO	1,4-Diazabicyclo[2,2,2]octane
DACH	*Trans*-1,2-diaminocyclohexane
DI	Deionized
DIBALH	Diisobutyl aluminum hydride
DME	1,2-Dimethoxyethane
DMEDA	*N,N*-Dimethylethylenediamine
DMF	*N,N*-Dimethylformamid
DMPA	2,2-Dimethoxy-2-phenylacetophenone
DMPU	1,3-Methyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
DPM	Methyl *trans*-2,5-dihydroxypent-3-enoate
DTBP	Di-*tert*-butyl peroxide
EDTA	Ethylenediaminetetraacetic acid
EPR	Electroparamagnetic resonance
Eqiuv.	Equivalent(s)
FCC	Fluid catalytic cracking
GC-Fid	Gas chromatography flame ionization detection
GCMS	Gas chromatography mass spectrometry
ICP-MS	Inductively coupled plasma mass spectrometry
IPC-OES	Inductively coupled plasma optical emission spectrometry
LiHMDS	Lithium bis(trimethylsilyl)amide

mol	Mole(s)
MTG	Methanol to gasoline
MVG	Methyl 2-hydroxy-4-butenoate
NBS	*N*-bromosuccinimide
NMP	*N*-methylpyrrolidone
NMR	Nuclear magnetic resonance
PEG	Polyethylene glycol
PLA	Poly(lactic acid)
ppb	Parts per billion
ppm	Parts per million
rt	Room temperature
SET	Single electron transfer
sm	Starting material
TASF	Tris(diethylamino)sulfonium difluorotrimethylsilicate
TBAB	Tetrabutylammonium bromide
TBAT	Tetrabutylammonium difluorotrimethylsilicate
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethyl(piperidine-1-yl)oxyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THM	*Trans*-2,5,6-trihydroxy-3-hexenoic acid methyl ester
THP	Tetrahydropyran
TLC	Thin layer chromatography
TON	Turn over number
UV	Ultraviolet (light)

Appendix C. Publications

Dimethylzinc-Initiated Radical Coupling of β-Bromostyrenes with Ethers and Amines

Sølvhøj, A.; Ahlburg, A.; Madsen, R. *Chem. Eur. J.* **2015**, *21*, 16272-16279

Manganese-Catalyzed Cross Coupling of Aryl Halides and Grignard Reagents by a Radical Mechanism

Antonacci, G.; Ahlburg, A.; Fristrup, P.; Norrby, P.-O.; Madsen, R. *Eur. J. Org. Chem.* **2017**, 4758-4764.

The Manganese-Catalyzed Cross-Coupling Reaction and the Influence of Trace Metals

Santilli, C.; Beigbaghlou, S. S.; Ahlburg, A.; Antonacci, G.; Fristrup, P.; Norrby, P.-O.; Madsen, R. *Eur. J. Org. Chem.* **2017**, 5269-5274.

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